WEST Search History

DATE: Friday, July 25, 2003

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,DWPI; PLUR=YES; OP=ADJ			
L9	cdc20	36	L9
L8	l5 and L7	85	L8
L7	tumor or cancer	167096	L7
L6	l2 same l3	7	L6
L5	l2 and l3	89	L5
L4	l2 and l3L3	0	L4
L3	mitosis	4729	L3
L2	mad	3758	L2
L1	mitosis near3 arrest near3 deficient	1	L1

END OF SEARCH HISTORY

=> d 60-144 bib,ab

L9 ANSWER 60 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:359441 BIOSIS
DN PREV200100359441
TI Mitotic checkpoints, genetic instability, and **cancer**.
AU Dobles, M. (1); Sorger, P. K. (1)
CS (1) Department of Biology, Massachusetts Institute of Technology, Cambridge, MA, 02139 USA
SO Cold Spring Harbor Laboratory Press. Cold Spring Harbor Symposia on Quantitative Biology, (2000) Vol. 65, pp. 361-368. Cold Spring Harbor Symposia on Quantitative Biology. Biological responses to DNA damage. print.
Publisher: Cold Spring Harbor Laboratory Press 10 Skyline Drive, Plainview, NY, 11803-2500, USA.
Meeting Info.: Cold Spring Harbor Symposia on Quantitative Biology Cold Spring Harbor, New York, USA
ISSN: 0091-7451. ISBN: 0-87969-605-2 (cloth), 0-87969-606-0 (paper).
DT Book; Conference
LA English
SL English

L9 ANSWER 61 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:356807 BIOSIS
DN PREV200100356807
TI Screen for small molecule inhibitors of the **spindle** assembly **checkpoint**.
AU Hoyt, Jonathan L. (1); King, Randall W.
CS (1) Harvard Medical School, 250 Longwood Ave, SGM 604, Boston, MA, 02115 USA
SO Molecular Biology of the Cell, (Dec., 2000) Vol. 11, No. Supplement, pp. 36a. print.
Meeting Info.: 40th American Society for Cell Biology Annual Meeting San Francisco, CA, USA December 09-13, 2000
ISSN: 1059-1524.
DT Conference
LA English
SL English

L9 ANSWER 62 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:314522 BIOSIS
DN PREV200100314522
TI p210bcr/abl is involved in a microtubule-damage cell cycle **checkpoint**.
AU Gelfanov, Vasily M. (1); Mantel, Charlie; Broxmeyer, Hal E.; Boswell, H. Scott (1)
CS (1) Medicine (Hematology/Oncology), Indiana University Purdue University, Indianapolis, IN USA
SO Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 459a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology
. ISSN: 0006-4971.
DT Conference
LA English
SL English
AB The oncogenic fusion gene product, BCR-ABL, generated by the Philadelphia chromosome and associated with CML and ALL, is a protein tyrosine kinase with myriad functions that are still incompletely documented. In addition to its proliferation-promoting ability, it has been implicated in resistance of CML cells to the apoptosis-inducing effects of radiation or of certain chemotherapy agents such as etoposide. There is a paucity of information on the potential involvement of BCR-ABL in cell cycle

checkpoints, which are considered to be primary targets of many **cancer** treatment strategies. We have previously investigated the mitotic **spindle checkpoint** and the newly discovered G1-phase microtubule (MT)-damage **checkpoint** (G1MTC) in several human and mouse primary cells and cell lines (Blood 1999;93,1390). We now report that human and mouse cell lines which overexpress p210bcr/abl are more sensitive to the G1-phase arresting effects of two MT damaging agents nocodazole and taxol. We used multivariate-intracellular labeling flow-cytometric cell cycle analysis and immunoblotting to evaluate the intracellular content of cyclins-A, B1, cdc-2, cdk-2, bcl-2, p21waf-1, and other cell cycle regulating molecules during different phases of the cell cycle in human MO7e and mouse H7 cells expressing BCR-ABL. Based on the intracellular content of these proteins, along with cell morphology and mitotic-index measurements, all the data support the notion that p210bcr/abl overexpressing cells had a greater G1-arrest response to MT damaging agents than did parental cells. This was associated with a dramatically increased expression of p21waf-1 in treated cells. The metaphase arrest/**spindle checkpoint** appeared to be intact in these cells since no cells expressing BCR-ABL were observed that have prematurely exited mitosis without cytokinesis (such as 4N/cyclin B1-negative cells or cells with polyploidy). The increased G1 arrest of BCR-ABL expressing cells could not be explained by changes in the apoptotic response to these agents. The mechanism of the MT damage-induced G1-arrest is unknown, however based on the decreased ratio of 2N-cdc-2-high/2N-cdc-2-low cells during G1 arrest, the mechanism likely involves the newly described G1MTC. Such an enhanced G1-phase arrest caused by the activation of the G1MTC in p210bcr/abl expressing cells responding to MT damage as that induced by certain chemotherapy agents has potential significance for therapeutic use of these agents in leukemia caused by p210bcr/abl.

L9 ANSWER 63 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:312146 BIOSIS
DN PREV200100312146
TI p21 waf-1 has a direct role in the human **spindle checkpoint**, but not in the mouse **checkpoint**.
AU Mantel, C. (1); Braun, S. (1); Lee, Y. (1); Kim, Y.-J. (1); Broxmeyer, H. E. (1)
CS (1) Dept. Microbiology/Immunology, Walther Oncology Center, Indiana University School of Medicine and Walther Cancer Institute, Indianapolis, IN USA
SO Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 700a. print. Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology
. ISSN: 0006-4971.
DT Conference
LA English
SL English
AB Our previous work suggested that the cell cycle **checkpoint** protein, p21waf-1 (p21), was involved in cell cycle arrest by the mitotic **spindle** assembly **checkpoint** (SAC) after microtubule/**spindle** (MTSP) disruption by nocodazole (Blood 1999;93,1390). However, the SAC has recently been evaluated in embryonic fibroblasts from mice with the p21 gene deleted (p21-/-), with the finding that p21 is not required for the SAC, but is required to prevent re-replication of chromosomes after mitotic slippage (**checkpoint** adaptation) caused by prolonged metaphase arrest after MTSP disruption (Mol. Cell. Biol. 1998;18,1055). We have now used intracellular labeling coupled with multivariate flow-cytometric cell cycle analysis to evaluate mitotic exit in p21-deficient human cell lines and also in proliferating mouse T-lymphocytes from p21-/- mice. Based on the expression of cdc2, cdk2, cyclins A, B1, D1, and MPM-2 proteins during the cell cycle, we report that human p21 deficient cells exit MTSP-induced metaphase arrest prior to

their p21-competent counterpart cells. This premature mitotic exit is accompanied by cdk, cyclin, and MPM-2 protein degradation and chromatin decondensation while remaining 4N in DNA content, hallmarks of cells that have undergone mitotic slippage without cytokinesis. In addition, these cells have a tendency to become polycentrosomal and polyploid. Similar experiments performed with proliferating splenic-derived T-lymphocytes from p21-/- mice do not display this behavior, nor do their wild type counterpart cells. These data are not explained by enhanced survival after MTSP disruption because the human p21 deficient cell lines and the p21-/- T-lymphocytes are more sensitive to MTSP induced apoptosis than their p21-competent counterparts as measured by annexin binding and caspase-3 activation assays. We suggest that p21 plays a much more important role in human cell cycle checkpoints, especially the SAC, than in the mouse. Considering the link between SAC defects and human **cancer**, further evaluation of the role of p21 in the human SAC is needed.

L9 ANSWER 64 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:311908 BIOSIS
DN PREV200100311908
TI A new interphase microtubule damage **checkpoint** defines an S-phase/chromosome replication commitment point: Involvement of p21WAFL and CDC2.
AU Mantel, C. (1); Braun, S. (1); Lee, Y. (1); Kim, Y.-J. (1); Broxmeyer, H. E. (1)
CS (1) Dept. Microbiology/Immunology, Walther Oncology Center, Indiana University School of Medicine and Walther Cancer Institute, Indianapolis, IN USA
SO Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 539a. print. Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology
. ISSN: 0006-4971.
DT Article; Conference
LA English
SL English
AB Cell cycle checkpoints assure orderly progression of events during cell division. **Checkpoint** defects, due to mutated, overexpressed, or missing **checkpoint** regulating proteins, are believed to contribute highly to the origin of genetic instability, a hallmark of human **cancer**. They are therefore, not surprisingly, frequently the targets of many chemotherapeutic treatment strategies for this disease. We previously described a new microtubule damage (MTD)-induced **checkpoint** in G1 phase of the cell cycle (G1MTC) for which little is known (Blood 1999:93, 1390). This work presented evidence of the existence of the G1MTC and suggested the involvement of the **checkpoint** protein, p21waf-1. Using an improved flow-cytometric cell cycle analysis method, we now show that the G1MTC is intact in activated T-lymphocytes from mice with the p21waf-1 gene deleted and therefore is dispensable for the G1MTC. However, p21waf-1 deletion does affect the ratio of cells that arrest at the G1MTC and the **spindle checkpoint** after MTD and is therefore indirectly involved in the G1MTC. The G1MTC arrests proliferating T-lymphocytes in G1 prior to cdc2 upregulation, and prior to G1 arrest by p21waf-1. Once cells have progressed past the G1MTC, they are committed to chromosome replication and metaphase progression, even in the presence of extreme MTD. The G1MTC is therefore a heretofore-unknown S-phase/chromosome replication commitment point. The G1MTC is also present in a human myeloid cell line deficient in p21waf-1 expression. The data and interpretation advanced here could not be explained by increased survival of p21-deficient cells in-vitro after MTD. In fact, annexin-binding and caspase-3 activation assays showed that p21 deficient cells were more sensitive to the apoptosis-inducing effects of MTD. The p21-independent G1MTC may be important in cellular responses to MTD such as that induced by drugs used to treat **cancer**. Its status in human tumors therefore requires

further evaluation.

L9 ANSWER 65 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:300033 BIOSIS
DN PREV200100300033
TI Impaired mitotic **checkpoint** in HTLV-I transformed cell lines: Implications for chemotherapeutics of adult T-cell leukemia.
AU Kasai, Takefumi (1); Iha, Hidekatsu (1); Iwanaga, Yoichi (1); Jeang, Kuan-Teh (1)
CS (1) NIH, 9000 Rockville Pike, Bethesda, MD, 20892 USA
SO FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A514. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DT Conference
LA English
SL English
AB Human T-lymphotropic virus type I (HTLV-I) causes adult T-cell leukemia (ATL). ATL cells contain extensive aneugenic and clastogenic chromosomal abnormalities. It is generally accepted that HTLV-I encodes a 40 kDa Tax oncoprotein. Tax has been described to affect cellular factors that control orderly cell cycle progression. It was suggested that Tax could influence via p53 the G1 to S phase transition and the DNA damage sentinel at this juncture. Recently, we have defined the mitotic **spindle** assembly **checkpoint** protein HsMad1 as a target for Tax. To check that loss of HsMad1 **spindle** assembly **checkpoint** function might explain the extensive aneuploidy observed in ATL cells, we examined mitotic regulation in six HTLV-I transformed cell lines using nocodazole, which is an microtubule-interfering agent (MIA) that disrupts assembly and activates the mitotic **spindle** assembly **checkpoint**. After treatment with nocodazole, all six ATL cells showed significantly reduced mitotic indices when compared to control cells. At the same time, four of these cells exhibited increased resistance to the development of apoptosis as induced by prolonged nocodazole treatment. In Western blotting assays, HTLV-I transformed cell lines compared to control cells had reduced amount of Mad1 and Mad2 in the nucleus when cells were treated with nocodazole. This finding suggests that the viral oncoprotein prevents function by abrogating proper subcellular localization of mitotic **checkpoint** proteins, Mad1 and Mad2. Accordingly, Tax-induced impairment of mitotic **checkpoint** might allow HTLV-I transformed cells to enter anaphase without correction of aneugenic damages. These defects in the mitotic **checkpoint** predict an insensitivity of ATL cells to MIAs such as nocodazole or vincristine. From the view point of mechanism-based therapy, the current findings of mitotic **checkpoint** defect suggest that antimicrotuble drugs such as vincristine should not be a first-line choice for therapeutic treatment of ATL.

L9 ANSWER 66 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:299994 BIOSIS
DN PREV200100299994
TI Expression of hBUB1 in acute myeloid leukemia.
AU Lin, Sheng-Fung (1); Lin, Pai-Mei; Yang, Ming-Chi (1); Liu, Ta-Chih (1); Chang, Jan-Gowth; Sue, Yu-Chieh (1); Chen, Tyen-Po (1)
CS (1) Division of Hematology-Oncology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Taiwan
SO Blood, (November 16, 2000) Vol. 96, No. 11 Part 2, pp. 193b. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology
. ISSN: 0006-4971.
DT Conference
LA English

SL English
AB Genetic instability has long been postulated of driving an elevated mutation rate and proposed to account for the mutation load found in human **cancer**. In most cancers, the instability is observed at the chromosome level, resulting in abnormal chromosome number. One of the mechanisms leading to aneuploidy is the disruption of the **spindle** assembly machinery. hBUB1 gene is a component of the mitotic **checkpoint** that monitors proper assembly of mitotic spindles, and the alteration of hBUB1 gene has been found to be associated with chromosomal instability in some **tumor** cell lines. We analyzed the coding region of hBUB1 by single strand conformational polymorphism (SSCP), complete sequence analysis and the expression of the hBUB1 gene by reverse transcription polymerase chain reaction (RT-PCR) in 92 AML specimens and 5 hematopoietic cell lines. A thymine/cytosine polymorphism at 8 bp upstream of 5' splice acceptor site of exon 10 was observed in Raji cell line and two AML specimens without a resultant change in the expression of hBUB1. Reductive expression and aberrant transcription of hBUB1 gene were detected in AML specimens by RT-PCR analysis, which may affect the control of mitotic **checkpoint**. Our study indicated that the mutation of hBUB1 gene is a rare event in leukemia specimens, and the post-transcriptional modification of hBUB1 has been shown to be the alteration in leukemogenesis.

L9 ANSWER 67 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:292618 BIOSIS
DN PREV200100292618
TI Chromosomal instability syndrome of total premature chromatid separation with mosaic variegated aneuploidy is defective in mitotic **spindle checkpoint**.
AU Matsuura, Shinya (1); Ito, Emi (1); Tauchi, Hiroshi (1); Ikeuchi, Tatsuro; Kajii, Tadashi; Komatsu, Kenshi (1)
CS (1) Dept. Rad. Biol., Hiroshima Univ., Hiroshima Japan
SO Journal of Radiation Research, (December, 2000) Vol. 41, No. 4, pp. 476. print.
Meeting Info.: 43rd Annual Meeting of the Japan Radiation Research Society Tokyo, Japan August 30-September 02, 2000
ISSN: 0449-3060.
DT Conference
LA English
SL English

L9 ANSWER 68 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:280644 BIOSIS
DN PREV200100280644
TI High expression of the proliferation and apoptosis associated CSE1L/CAS gene in hepatitis and liver neoplasms: Correlation with **tumor** progression.
AU Wellmann, A.; Flemming, P.; Behrens, P.; Wuppermann, K.; Lang, H.; Oldhafer, K.; Pastan, I.; Brinkmann, U. (1)
CS (1) Pharmacogenetics Lab, Epidauros Biotechnology, Am Neuland 1, D-82347, Bernried: uli@epidauros.com Germany
SO International Journal of Molecular Medicine, (May, 2001) Vol. 7, No. 5, pp. 489-494. print.
ISSN: 1107-3756.
DT Article
LA English
SL English
AB The CSE1L/CAS protein (CAS) is a Ran-binding protein with a function as nuclear transport (export) factor. Like recently observed for ran and other ran-binding proteins, CSE1L/CAS simultaneously plays a role in the mitotic **spindle checkpoint**, which assures genomic stability during cell division. This **checkpoint** is frequently disturbed in neoplasias of various origin, including hepatic tumors. We have evaluated by immunohistology the expression of CAS in adult and

embryonic liver, hepatitis, and in liver hyperplasias. Normal hepatocytes revealed no CAS expression while embryonic liver showed strong expression in all parenchymal cells. Bile ducts stained positive with anti-CAS antibodies, and strong CAS expression was also detected at the interface between bile ducts and hepatocytes under conditions associated with regenerative proliferation. The localization of these CAS expressing cells correlated with the distribution of 'oval' putative liver stem-cells. In active viral (but not in inactive) hepatitis, strong hepatocytal CAS expression correlates in site and intensity with degree of inflammation. Neoplastic liver demonstrated different degrees of CAS expression: no remarkable expression in adenomas, moderate expression in a narrow rim of hepatocytes and in periseptal cholangiolar proliferations in focal nodular hyperplasia, and strong CAS expression in hepatocellular carcinoma. Less differentiated tumors stain stronger than well differentiated. Cholangio-cellular carcinomas show even stronger CAS expression than hepatocellular carcinomas. Our observation of strong expression of CAS in liver cells that are committed for proliferation among them possibly liver stem cells, and in liver neoplasms, is consistant with the fact that CAS functions not solely as a nuclear transport factor but that it is also essential for cell proliferation, particularly for the mitotic **spindle checkpoint**. Interestingly, genomic instability is frequently observed in hepatic tumors which we have shown here to express large amounts of CAS. Since the degree of CAS-expression correlates with the grade of **tumor** dedifferentiation, we suggest that CAS should also be further investigated as prognostic marker for hepatic neoplasms.

L9 ANSWER 69 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:266991 BIOSIS
DN PREV200100266991
TI Mutation analysis of hBUB1, hBUBR1 and hBUB3 genes in glioblastomas.
AU Reis, Rui M.; Nakamura, Mitsutoshi; Masuoka, Jun; Watanabe, Takao; Colella, Stefano; Yonekawa, Yasuhiro; Kleihues, Paul; Ohgaki, Hiroko (1)
CS (1) International Agency for Research on Cancer, 150 cours Albert Thomas, 69372, Lyon Cedex, 08: ohgaki@iarc.fr France
SO Acta Neuropathologica, (April, 2001) Vol. 101, No. 4, pp. 297-304. print. ISSN: 0001-6322.
DT Article
LA English
SL English
AB Glioblastomas, the most malignant human brain tumors, are characterized by marked aneuploidy, suggesting chromosomal instability which may be caused by a defective mitotic **spindle checkpoint**. We screened 22 glioblastomas for mutations in the mitotic **spindle checkpoint** genes hBUB1, hBUBR1 and hBUB3. DNA sequencing revealed a silent mutation at codon 144 of hBUB1 (CAGfwdarwCAA, GlnfwdarwGln) in one glioblastoma, a silent mutation at codon 952 of hBUBR1 (GACfwdarwGAT, AspfwdarwAsp) in another glioblastoma, and a silent mutation at codon 388 of the hBUBR1 gene (GCGfwdarwGCA, AlafwdarwAla) in 8 glioblastomas. We also observed a known polymorphism at hBUBR1 codon 349 (CAA/CGA, Gln/Arg), with an allelic frequency of 0.75 for Gln and 0.25 for Arg, which is similar to that among healthy Caucasian individuals (0.73 vs 0.27). The coding sequence of the hBUB3 gene did not contain any mutation, but in 4 glioblastomas (18%), a CfwdarwT point mutation was detected at position -6 (6 nucleotides upstream of the ATG initiator codon). Analysis of blood DNA of these patients showed identical sequence alterations, indicating that this is a polymorphism. Again, the frequency in glioblastomas was similar to that in healthy Caucasians (15%). We further screened hBUB1 in 18 cases of giant cell glioblastoma, a variant characterized by a predominance of bizarre, multinucleated giant cells. There were no changes, except for a silent mutation at codon 144 in two cases. These results suggest that mutations in these mitotic **spindle checkpoint** genes do not play a significant role in the causation of chromosomal instability in glioblastomas.

L9 ANSWER 70 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:264732 BIOSIS
DN PREV200100264732
TI **Checkpoint** genes in **cancer**.
AU McDonald, E. Robert, III; El-Deiry, Wafik S. (1)
CS (1) University of Pennsylvania, 415 Curie Blvd, CRB 437, Philadelphia, PA, 19104: wafik@mail.med.upenn.edu USA
SO Annals of Medicine, (March, 2001) Vol. 33, No. 2, pp. 113-122. print.
ISSN: 0785-3890.
DT Article
LA English
SL English
AB The mammalian cell cycle is exquisitely controlled by a 'machinery' composed of cyclin-dependent kinases and their binding partners, the cyclins. These kinases regulate transitions into DNA synthesis and mitosis, and their inactivity contributes to cellular quiescence, differentiation and senescence. Cell cycle transitions are, in turn, controlled by checkpoints that monitor ribonucleotide pools, oxygen tension, the extracellular environment, growth signalling programmes, the status of DNA replication, and the mitotic **spindle** apparatus. Genes positively controlling cell cycle checkpoints can be targets for oncogenic activation in **cancer**, whereas negative regulators, such as **tumour** suppressor genes, are targeted for inactivation. Understanding the molecular details of cell cycle regulation and **checkpoint** abnormalities in **cancer** offers insight into potential therapeutic strategies.

L9 ANSWER 71 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:242646 BIOSIS
DN PREV200100242646
TI Molecular cloning of human MOB1, a factor involving in the mitotic **spindle checkpoint** pathway.
AU Tatsuka, Masaaki (1); Suto, Shiho (1); Katayama, Hiroshi (1); Han, Zhen-Bo (1); Suzuki, Fumio (1)
CS (1) Res. Inst. Radiat. Biol. Med., Hiroshima Univ., Hiroshima Japan
SO Journal of Radiation Research, (December, 2000) Vol. 41, No. 4, pp. 404. print.
Meeting Info.: 43rd Annual Meeting of the Japan Radiation Research Society Tokyo, Japan August 30-September 02, 2000
ISSN: 0449-3060.
DT Conference
LA English
SL English

L9 ANSWER 72 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:198906 BIOSIS
DN PREV200100198906
TI Four single-nucleotide polymorphisms in the human BUB1 gene.
AU Kanbe, Takamasa; Nobukuni, Takahiro; Kawasaki, Hironaka; Sekiya, Takao; Murakami, Yoshinori (1)
CS (1) Tumor Suppression and Functional Genomics Project, National Cancer Center Research Institute, 5-1-1 Tsukiji, Chuo-ku, Tokyo, 104-0045: ymurakam@gan2.ncc.go.jp Japan
SO Journal of Human Genetics, (2001) Vol. 46, No. 3, pp. 150-151. print.
ISSN: 1434-5161.
DT Article
LA English
SL English
AB Four single-nucleotide polymorphisms have been found in the human BUB1 gene, which encodes a kinase involved in the mitotic **spindle checkpoint**. A cytosine-to-thymine change in exon 10, corresponding to codon 375 (c.1124C>T), causes an amino acid substitution of serine to phenylalanine. A guanine/cytosine polymorphism in exon 4 (c.279G>C) and a

thymine/cytosine polymorphism in exon 12 (c.1293T>C) do not cause amino acid substitution. The other polymorphism, of thymine/cytosine (IVS9-8T>C), is found at 8 bp upstream of exon 10. As mutations of the hBUB1 gene were reported in a subset of human cancers, these polymorphisms could provide useful tools for the genetic study of susceptibility to various human cancers.

L9 ANSWER 73 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:164035 BIOSIS
DN PREV200100164035
TI Mitotic checkpoints: From yeast to **cancer**.
AU Wassmann, Katja; Benezra, Robert (1)
CS (1) Cell Biology Program, Memorial Sloan-Kettering Cancer Center and the Sloan-Kettering Division, Graduate School of Medical Sciences, Cornell University, 1275 York Avenue, New York, NY, 10021: r-benezra@ski.mskcc.org USA
SO Current Opinion in Genetics & Development, (February, 2001) Vol. 11, No. 1, pp. 83-90. print.
ISSN: 0959-437X.
DT General Review
LA English
SL English

L9 ANSWER 74 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:161129 BIOSIS
DN PREV200100161129
TI Mitogen-induced p53 downregulation precedes vascular smooth muscle cell migration from healthy tunica media and proliferation.
AU Rodriguez-Campos, Antonio; Ruiz-Enriquez, Pilar; Faraudo, Susanna; Badimon, Lina (1)
CS (1) IIBB-CSIC, Jordi Girona, 18-26, 08034, Barcelona: lbmucv@cid.csic.es Spain
SO Arteriosclerosis Thrombosis and Vascular Biology, (February, 2001) Vol. 21, No. 2, pp. 214-219. print.
ISSN: 1079-5642.
DT Article
LA English
SL English
AB The **tumor** suppressor protein p53 plays an important role in the cell-cycle G1 and G2 checkpoints. In response to DNA damage, p53 can induce the transcription of p21, which inhibits the activation of various G1 cyclin/cyclin-dependent kinase complexes. It is not known whether p53 plays a role in the initial migration of vascular smooth muscle cells from the arterial tunica media (mVSMCs). In this study, we have investigated whether mVSMC migration from healthy tunica media of young pigs and proliferation are regulated by p53. After 6 hours of incubation in mitogen-rich medium, explanted porcine tunica media tissue showed complete downregulation of p53 protein and p53 mRNA. The blockage of gene activity was not due to DNA methylation at the 5' control region of the gene. The mVSMC outgrowth did not show p53 expression. Mitogen-depletion of cultured p53-/mVSMCs did not restore p53 expression. Incubation of explanted porcine tunica media tissue in mitogen-deprived medium increased p53 protein content and blocked mVSMC outgrowth from the explant. As in p53-deficient rodent cells, mVSMCs incubated with colcemid overrode the **spindle**-dependent **checkpoint**, giving polyploidy and chromosomal pairing. UV-induced DNA damage in mVSMCs incubated with mitogen-free medium induced p53 expression and apoptotic cell death showing DNA nucleosomal laddering. However, UV-irradiated mVSMCs incubated in mitogen-rich medium did not express p53 and did not show cell death. In conclusion, our results demonstrate that early mVSMC migration from the tunica media requires mitogen-induced suppression of p53 that is highly expressed in contractile mVSMCs residing in the healthy vessel wall.

L9 ANSWER 75 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

AN 2001:157261 BIOSIS
DN PREV200100157261
TI Characterisation of the human APC1, the largest subunit of the anaphase-promoting complex.
AU Jorgensen, P. M.; Graslund, S.; Betz, R.; Stahl, S.; Larsson, C.; Hoog, C. (1)
CS (1) Department of Cell and Molecular Biology, Nobels vag 3, S-171 77, Stockholm: christer.hoog@cmb.ki.se Sweden
SO Gene (Amsterdam), (10 January, 2001) Vol. 262, No. 1-2, pp. 51-59. print. ISSN: 0378-1119.
DT Article
LA English
SL English
AB Accurate segregation of sister chromatids during mitosis is necessary to avoid the aneuploidy found in many cancers. The **spindle checkpoint**, which monitors the metaphase to anaphase transition, has been shown to be defective in cancers with chromosomal instability. This **checkpoint** regulates the anaphase-promoting complex or cyclosome (APC/C), a cell cycle ubiquitin ligase regulating among other things sister chromatid separation. We have previously investigated the mouse Apc1 protein (previously also called Tsg24), the largest subunit of the APC/C. We have now sequenced a full-length human APC1 cDNA, mapped its chromosomal location, and analysed its intron-exon boundaries. We have also investigated the RNA and protein expression of the Apc1 and other APC/C components in normal and **cancer** cells and the relative occurrence of expressed sequence tags (ESTs) representing APC subunits from different tissues. The different APC/C subunits are expressed in most tissues and cell types at fairly constant levels relative to each other, suggesting that they perform their functions as part of a complex. A difference from this pattern is however seen for the APC6, which in some cases is more strongly expressed, suggesting a special function for this protein in certain tissues and cell types.

L9 ANSWER 76 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:140887 BIOSIS
DN PREV200100140887
TI The interphase microtubule damage **checkpoint** defines an S-phase commitment point and does not require p21waf-1.
AU Mantel, Charlie R. (1); Braun, Stephen E.; Lee, Younghee; Kim, Young-June; Broxmeyer, Hal E.
CS (1) Walther Oncology Center, 1044 West Walnut St, Indianapolis, IN, 46202-5121: cmantel@iupui.edu USA
SO Blood, (March, 2001) Vol. 97, No. 5, pp. 1505-1507. print. ISSN: 0006-4971.
DT Article
LA English
SL English
AB Cell cycle checkpoints ensure orderly progression of events during cell division. A microtubule damage (MTD)-induced **checkpoint** has been described in G1 phase of the cell cycle (G1MTC) for which little is known. The present study shows that the G1MTC is intact in activated T lymphocytes from mice with the p21waf-1 gene deleted. However, p21waf-1 gene deletion does affect the ratio of cells that arrest at the G1MTC and the **spindle checkpoint** after MTD. The G1MTC arrests T lymphocytes in G1 prior to cdc2 up-regulation and prior to G1 arrest by p21waf-1. Once cells have progressed past the G1MTC, they are committed to chromosome replication and metaphase progression, even with extreme MTD. The G1MTC is also present in a human myeloid cell line deficient in p21waf-1 gene expression. The p21-independent G1MTC may be important in cellular responses to MTD such as those induced by drugs used to treat **cancer**.

L9 ANSWER 77 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:93661 BIOSIS

DN PREV200100093661
TI MAD2 haplo-insufficiency causes premature anaphase and chromosome instability in mammalian cells.
AU Michel, Loren S.; Liberal, Vasco; Chatterjee, Anupam; Kirchwegger, Regina; Pasche, Boris; Gerald, William; Dobles, Max; Sorger, Peter K.; Murty, V. V. V. S.; Benezra, Robert (1)
CS (1) Cell Biology and Genetics Program, Graduate School of Medical Sciences, Sloan-Kettering Division, Memorial Sloan-Kettering Cancer Center, Cornell University, New York, NY, 10021: r-benezra@ski.mskcc.org USA
SO Nature (London), (18 January, 2001) Vol. 409, No. 6818, pp. 355-359. print.
ISSN: 0028-0836.
DT General Review
LA English
SL English
AB The mitotic **checkpoint** protein hsMad2 is required to arrest cells in mitosis when chromosomes are unattached to the mitotic **spindle**. The presence of a single, lagging chromosome is sufficient to activate the **checkpoint**, producing a delay at the metaphase-anaphase transition until the last **spindle** attachment is made. Complete loss of the mitotic **checkpoint** results in embryonic lethality owing to chromosome mis-segregation in various organisms. Whether partial loss of **checkpoint** control leads to more subtle rates of chromosome instability compatible with cell viability remains unknown. Here we report that deletion of one MAD2 allele results in a defective mitotic **checkpoint** in both human **cancer** cells and murine primary embryonic fibroblasts. **Checkpoint** -defective cells show premature sister-chromatid separation in the presence of **spindle** inhibitors and an elevated rate of chromosome mis-segregation events in the absence of these agents. Furthermore, Mad2+/- mice develop lung tumours at high rates after long latencies, implicating defects in the mitotic **checkpoint** in tumorigenesis.

L9 ANSWER 78 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:50365 BIOSIS
DN PREV200100050365
TI Waiting for anaphase: Mad2 and the **spindle** assembly **checkpoint**.
AU Shah, Jagesh V.; Cleveland, Don W. (1)
CS (1) Department of Cellular and Molecular Medicine, University of California at San Diego, La Jolla, CA, 92093: dcleveland@ucsd.edu USA
SO Cell, (December 22, 2000) Vol. 103, No. 7, pp. 997-1000. print.
ISSN: 0092-8674.
DT General Review
LA English
SL English

L9 ANSWER 79 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:49549 BIOSIS
DN PREV200100049549
TI The **spindle checkpoint** of Saccharomyces cerevisiae responds to separable microtubule-dependent events.
AU Daum, John R.; Gomez-Ospina, Natalia; Winey, Mark; Burke, Daniel J. (1)
CS (1) Department of Biochemistry and Molecular Genetics, University of Virginia Medical Center, Charlottesville, VA, 22908-0733: dburke@virginia.edu USA
SO Current Biology, (2 November, 2000) Vol. 10, No. 21, pp. 1375-1378. print.
ISSN: 0960-9822.
DT Article
LA English
SL English
AB The **spindle checkpoint** regulates microtubule-based

chromosome segregation and helps to maintain genomic stability (1,2). Mutational inactivation of **spindle checkpoint** genes has been implicated in the progression of several types of human **cancer**. Recent evidence from budding yeast suggests that the **spindle checkpoint** is complex. Order-of-function experiments have defined two separable pathways within the **checkpoint**. One pathway, defined by MAD2, controls the metaphase-to-anaphase transition and the other, defined by BUB2, controls the exit from mitosis (3-6). The relationships between the separate branches of the **checkpoint**, and especially the events that trigger the pathways, have not been defined. We localized a Bub2p-GFP fusion protein to the cytoplasmic side of the **spindle** pole body and used a kar9 mutant to show that cells with misoriented spindles are arrested in anaphase of mitosis. We used a kar9 bub2 double mutant to show that the arrest is BUB2 dependent. We conclude that the separate pathways of the **spindle checkpoint** respond to different classes of microtubules. The MAD2 branch of the pathway responds to kinetochore microtubule interactions and the BUB2 branch of the pathway operates within the cytoplasm, responding to **spindle** misorientation.

L9 ANSWER 80 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:45527 BIOSIS
DN PREV200100045527
TI UkrainTM, a semisynthetic Chelidonium majus alkaloid derivative, acts by inhibition of tubulin polymerization in normal and malignant cell lines.
AU Panzer, A.; Hamel, E.; Joubert, A. M. (1); Bianchi, P. C.; Seegers, J. C.
CS (1) Department of Physiology, University of Pretoria, Pretoria, 0001: ajoubert@postillion.up.ac.za South Africa
SO Cancer Letters, (November 28, 2000) Vol. 160, No. 2, pp. 149-157. print. ISSN: 0304-3835.
DT Article
LA English
SL English
AB UkrainTM has been described as a semisynthetic Chelidonium majus alkaloid derivative, which exhibits selective toxicity towards malignant cells only. Its mechanism of action has hitherto been uncertain. We found that UkrainTM inhibits tubulin polymerization, leading to impaired microtubule dynamics. This results in activation of the **spindle checkpoint** and thus a metaphase block. The effects of UkrainTM on the growth, cell cycle progression and morphology of two normal, two transformed and two malignant cell lines did not differ. We could thus find no evidence for the selective cytotoxicity previously reported for UkrainTM.

L9 ANSWER 81 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:21050 BIOSIS
DN PREV200100021050
TI Mammalian recombination-repair genes XRCC2 and XRCC3 promote correct chromosome segregation.
AU Griffin, Carol S.; Simpson, Paul J.; Wilson, Caroline R.; Thacker, John (1)
CS (1) Radiation and Genome Stability Unit, MRC, Harwell, Oxfordshire, OX11 0RD: j.thacker@har.mrc.ac.uk UK
SO Nature Cell Biology, (October, 2000) Vol. 2, No. 10, pp. 757-761. print. ISSN: 1465-7392.
DT Article
LA English
SL English
AB Growth and development are dependent on the faithful duplication of cells. Duplication requires accurate genome replication, the repair of any DNA damage, and the precise segregation of chromosomes at mitosis; molecular checkpoints ensure the proper progression and fidelity of each stage. Loss of any of these highly conserved functions may result in genetic instability and proneness to **cancer**. Here we show that highly

significant increases in chromosome missegregation occur in cell lines lacking the RAD51-like genes XRCC2 and XRCC3. This increased missegregation is associated with fragmentation of the centrosome, a component of the mitotic **spindle**, and not with loss of the **spindle checkpoint**. Our results show that unresolved DNA damage triggers this instability, and that XRCC2 and XRCC3 are potential **tumour**-suppressor genes in mammals.

L9 ANSWER 82 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:20046 BIOSIS
DN PREV200100020046
TI Expression and mutational analyses of the human MAD2L1 gene in breast **cancer** cells.
AU Percy, Melanie J.; Myrie, Kenute A.; Neeley, Christopher K.; Azim, James N.; Ethier, Stephen P.; Petty, Elizabeth M. (1)
CS (1) Department of Internal Medicine, Division of Medical Genetics, University of Michigan, 1150 West Medical Center Drive, 4301 MSRB III, Ann Arbor, MI, 48109: epetty@umich.edu USA
SO Genes Chromosomes & Cancer, (December, 2000) Vol. 29, No. 4, pp. 356-362. print.
ISSN: 1045-2257.
DT Article
LA English
SL English
AB Breast **cancer** is a heterogeneous disorder in which most tumors display some degree of aneuploidy, especially those at later stages of the disease. Aneuploidy and associated chromosome instability may be important in the progression of mammary tumorigenesis. Aneuploidy is prevented during normal cell division in part through regulation of a mitotic **spindle checkpoint** where mitotic arrest prevents segregation of misaligned chromosomes into daughter cells at anaphase. Mitotic arrest genes, including the MAD family, which was originally characterized in yeast, help regulate normal function of the mitotic **spindle checkpoint**. Decreased expression of the human gene MAD2L1 was previously reported in a breast **cancer** cell line exhibiting chromosome instability and aneuploidy. To explore further the potential role of MAD2L1 in breast **cancer**, we analyzed MAD2L1 gene expression in 13 minimally to grossly aneuploid human breast **cancer** cell lines and found significant differences of expression in three lines. Sequence analysis of MAD2L1 cDNA in these as well as nine additional aneuploid breast **cancer** and five immortalized normal human mammary epithelial cell lines revealed one heterozygous frameshift (572 del A) mutation in a **cancer** cell line that demonstrated a high level of transcript expression. In addition, two 3'UTR sequence variants were noted in breast **cancer** cell lines. The 572 del A mutation creates a truncated MAD2 protein product. Further functional studies in primary breast tumors are therefore warranted to determine the potential role MAD2L1 may play in breast **cancer**.

L9 ANSWER 83 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:534056 BIOSIS
DN PREV200000534056
TI Cell cycle checkpoints and their inactivation in human **cancer**.
AU Molinari, M. (1)
CS (1) European Institute of Oncology, 435 Via Ripamonti, 20141, Milan Italy
SO Cell Proliferation, (October, 2000) Vol. 33, No. 5, pp. 261-274. print.
ISSN: 0960-7722.
DT Article
LA English
SL English
AB Checkpoints are mechanisms that regulate progression through the cell cycle insuring that each step takes place only once and in the right sequence. Mutations of **checkpoint** proteins are frequent in all types of **cancer** as defects in cell cycle control can lead to

genetic instability. This review will focus on three major areas of cell cycle transition control, with particular attention to the alterations found in human **cancer**. These areas include the G1/S transition, where most **cancer**-related defects occur, the G2/M **checkpoint** and its activation in response to DNA damage, and the **spindle checkpoint**.

L9 ANSWER 84 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:533782 BIOSIS
DN PREV200000533782
TI Mutations in the Plk gene lead to instability of Plk protein in human **tumour** cell lines.
AU Simizu, Siro; Osada, Hiroyuki (1)
CS (1) Antibiotics Laboratory, RIKEN, Hirosawa 2-1, Wako, Saitama, 351-0198 Japan
SO Nature Cell Biology, (November, 2000) Vol. 2, No. 11, pp. 852-854. print. ISSN: 1465-7392.
DT Article
LA English
SL English
AB It has been established that mutations in Drosophila Polo cause abnormalities in mitosis. In human cells, maximal Plk activity is reached in the M phase of the cell cycle, and the function of Plk is therefore considered to be required for mitotic cellular events such as **spindle** formation, chromosome segregation and cytokinesis. Microinjection of anti-Plk antibody into living cells has been found to induce a mitotic abnormality that contributes to the generation of aneuploidy, and this is an important finding in relation to **tumour** development. Indeed, previous studies have shown that the level of expression of a mitotic **checkpoint** gene, hsMAD2, is reduced and that another **checkpoint** gene, BUB1, is mutated in certain human **cancer** cells.

L9 ANSWER 85 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:485046 BIOSIS
DN PREV200000485046
TI Novel actions of the antitumor drugs vinflunine and vinorelbine on microtubules.
AU Ngan, Vivian K.; Bellman, Krista; Panda, Dulal; Hill, Bridget T.; Jordan, Mary Ann; Wilson, Leslie (1)
CS (1) Department of Molecular, Cellular, and Developmental Biology, University of California, Santa Barbara, CA, 93106 USA
SO Cancer Research, (September 15, 2000) Vol. 60, No. 18, pp. 5045-5051. print.
ISSN: 0008-5472.
DT Article
LA English
SL English
AB Vinflunine is a novel Vinca alkaloid presently in Phase I clinical trials. In preclinical studies, it exhibited superior antitumor activity to that of other Vinca alkaloids, including vinorelbine from which it was synthetically derived. Vinca alkaloids appear to inhibit cell proliferation by affecting the dynamics of **spindle** microtubules. Here we have analyzed the effects of vinflunine and vinorelbine on microtubule dynamic instability and treadmilling and found that these newer drugs exert effects on microtubule dynamics that differ significantly from those of the classic Vinca alkaloid, vinblastine. The major effects of vinflunine and vinorelbine on dynamic instability were a slowing of the microtubule growth rate, an increase in growth duration, and a reduction in shortening duration. In marked contrast to the action of vinblastine, they neither reduced the rate of shortening nor increased the percentage of time the microtubules spent in an attenuated state, neither growing nor shortening detectably. In addition, vinflunine and vinorelbine suppressed treadmilling, but less strongly than vinblastine.

The diverse actions of these drugs on microtubules are likely to produce different effects on mitotic **spindle** function, leading to different effects on cell cycle progression and cell killing. Nontumor cells with normal **checkpoint** proteins may tolerate the relatively less powerful inhibitory effects of vinflunine and vinorelbine on microtubule dynamics better than the more powerful effects of vinblastine. Thus the unique constellation of effects of vinflunine and vinorelbine on dynamic instability and treadmilling may contribute to their superior antitumor efficacies.

L9 ANSWER 86 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:452461 BIOSIS
DN PREV200000452461
TI Chromosomal instability syndrome of total premature chromatid separation with mosaic variegated aneuploidy is defective in mitotic-**spindle checkpoint**.
AU Matsuura, Shinya; Ito, Emi; Tauchi, Hiroshi; Komatsu, Kenshi (1); Ikeuchi, Tatsuro; Kajii, Tadashi
CS (1) Department of Radiation Biology, Research Institute for Radiation Biology and Medicine, Hiroshima University, Kasumi 1-2-3, Minamiku, Hiroshima, 734-8553 Japan
SO American Journal of Human Genetics, (August, 2000) Vol. 67, No. 2, pp. 483-486. print.
ISSN: 0002-9297.
DT Article
LA English
SL English
AB Skin fibroblast cells from two unrelated male infants with a chromosome-instability disorder were analyzed for their response to colcemid-induced mitotic-**spindle checkpoint**. The infants both had severe growth and developmental retardation, microcephaly, and Dandy-Walker anomaly; developed Wilms **tumor**; and one died at age 5 mo, the other at age 3 years. Their metaphases had total premature chromatid separation (total PCS) and mosaic variegated aneuploidy. Mitotic-index analysis of their cells showed the absence of mitotic block after the treatment with colcemid, a mitotic-**spindle** inhibitor. Bromodeoxyuridine-incorporation measurement and microscopic analysis indicated that cells treated with colcemid entered G1 and S phases without sister-chromatid segregation and cytokinesis. Preparations of short-term colcemid-treated cells contained those cells with chromosomes in total PCS and all or clusters of them encapsulated by nuclear membranes. Cell-cycle studies demonstrated the accumulation of cells with a DNA content of 8C. These findings indicate that the infants' cells were insensitive to the colcemid-induced mitotic-**spindle checkpoint**.

L9 ANSWER 87 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:449932 BIOSIS
DN PREV200000449932
TI Chfr defines a mitotic stress **checkpoint** that delays entry into metaphase.
AU Scolnick, Daniel M.; Halazonetis, Thanos D. (1)
CS (1) Wistar Institute, 3601 Spruce Street, Philadelphia, PA, 19104-4268 USA
SO Nature (London), (July 27, 2000) Vol. 406, No. 6794, pp. 430-435. print.
ISSN: 0028-0836.
DT Article
LA English
SL English
AB Chemicals that target microtubules induce mitotic stress by affecting several processes that occur during mitosis. These processes include separation of the centrosomes in prophase, alignment of the chromosomes on the **spindle** in metaphase and sister-chromatid separation in anaphase. Many human cancers are sensitive to mitotic stress. This sensitivity is being exploited for therapy and implies **checkpoint**

defects. The known mitotic **checkpoint** genes, which prevent entry into anaphase when the chromosomes are not properly aligned on the mitotic **spindle**, are, however, rarely inactivated in human **cancer** . Here we describe the chfr gene, which is inactivated owing to lack of expression or by mutation in four out of eight human **cancer** cell lines examined. Normal primary cells and **tumour** cell lines that express wild-type chfr exhibited delayed entry into metaphase when centrosome separation was inhibited by mitotic stress. In contrast, the **tumour** cell lines that had lost chfr function entered metaphase without delay. Ectopic expression of wild-type chfr restored the cell cycle delay and increased the ability of the cells to survive mitotic stress. Thus, chfr defines a **checkpoint** that delays entry into metaphase in response to mitotic stress.

L9 ANSWER 88 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:436898 BIOSIS
DN PREV200000436898
TI Genomic instability at the BUB1 locus in colorectal **cancer**, but not in non-small cell lung **cancer**.
AU Jaffrey, Ross G.; Pritchard, Stuart C.; Clark, Caroline; Murray, Graeme I.; Cassidy, James; Kerr, Keith M.; Nicolson, Marianne C.; McLeod, Howard L. (1)
CS (1) Washington University School of Medicine, Saint Louis, MO, 63110 USA
SO Cancer Research, (August 15, 2000) Vol. 60, No. 16, pp. 4349-4352. print.
ISSN: 0008-5472.
DT Article
LA English
SL English
AB Genomic instability is observed in the majority of human tumors. Dysregulation of the mitotic **spindle checkpoint** is thought to be one of the mechanisms that facilitate aneuploidy in **tumor** cells. Mutations in the mitotic **spindle checkpoint** kinase BUB1 cause a dominant negative disruption of the **spindle**, leading to chromosome instability in **cancer** cell lines. However, little is known about chromosome 2q14, the genomic region containing BUB1, in human tumors. The BUB1 locus was evaluated in 32 colorectal **cancer** (CRC) and 20 non-small cell lung **cancer** (NSCLC) primary tumors using a panel of seven microsatellite repeats for 2q, two CA repeats in BUB1, and gene mutation analysis. The 2q locus was allelically stable in NSCLC but relatively unstable in colorectal primary tumors (20 of 32 tumors, 62.5%). In addition, 14.5% of CRC patients displayed instability within BUB1. Previously described BUB1 mutations and polymorphisms were rare (<1%) in the CRC or NSCLC tumors. Our data demonstrate 2q and BUB1 allelic instability in CRC and indicate that mutations in BUB1 are rare causes of chromosome instability in CRC or NSCLC. Additional investigations may shed light on the mechanistic impact of the mitotic **spindle checkpoint** pathway in colorectal **tumor** initiation and progression.

L9 ANSWER 89 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:388637 BIOSIS
DN PREV200000388637
TI Gain of function properties of mutant p53 proteins at the mitotic **spindle** cell cycle **checkpoint**.
AU Hixon, M. L.; Flores, A.; Wagner, M.; Gualberto, A. (1)
CS (1) Department of Physiology and Biophysics, Case Western Reserve University School of Medicine, 10900 Euclid Ave., Cleveland, OH, 44106 USA
SO Histology and Histopathology, (April, 2000) Vol. 15, No. 2, pp. 551-556. print.
ISSN: 0213-3911.
DT General Review
LA English
SL English

AB Mutations in the p53 **tumor** suppressor gene locus predispose human cells to chromosomal instability. This is due in part to interference of mutant p53 proteins with the activity of the mitotic **spindle** and postmitotic cell cycle checkpoints. Recent data demonstrates that wild type p53 is required for postmitotic **checkpoint** activity, but plays no role at the mitotic **spindle checkpoint**. Likewise, structural dominant p53 mutants demonstrate gain-of-function properties at the mitotic **spindle checkpoint** and dominant negative properties at the postmitotic **checkpoint**. At mitosis, mutant p53 proteins interfere with the control of the metaphase-to-anaphase progression by up-regulating the expression of CKs1, a protein that mediates activatory phosphorylation of the anaphase promoting complex (APC) by Cdc2. Cells that carry mutant p53 proteins overexpress CKs1 and are unable to sustain APC inactivation and mitotic arrest. Thus, mutant p53 gain-of-function at mitosis constitutes a key component to the origin of chromosomal instability in mutant p53 cells.

L9 ANSWER 90 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:374812 BIOSIS
DN PREV200000374812
TI The delayed action of the **spindle checkpoint** in p53 mutated lymphoid **tumour** cells.
AU Ivanov, A. (1); Cragg, M. S.; Illidge, T. M.; Erenpreisa, Je (1)
CS (1) Laboratory of Tumour Cell Biology, University of Latvia, Riga Latvia
SO British Journal of Cancer, (July, 2000) Vol. 83, No. Supplement 1, pp. 58. print.
Meeting Info.: Meeting of the British Cancer Research Brighton, UK July 09-12, 2000
ISSN: 0007-0920.
DT Conference
LA English
SL English

L9 ANSWER 91 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:347675 BIOSIS
DN PREV200000347675
TI Kinetochore "memory" of **spindle checkpoint** signaling in lysed mitotic cells.
AU Campbell, Michael S.; Daum, John R.; Gersch, Michael S.; Nicklas, R. Bruce; Gorbsky, Gary J. (1)
CS (1) Department of Cell Biology, University of Oklahoma Health Sciences Center, 975 NE 10th St., Biomedical Research Building, Room 266, Oklahoma City, OK, 73104 USA
SO Cell Motility and the Cytoskeleton, (June, 2000) Vol. 46, No. 2, pp. 146-156. print.
ISSN: 0886-1544.
DT Article
LA English
SL English
AB The **spindle checkpoint** prevents errors in mitosis. Cells respond to the presence of kinetochores that are improperly attached to the mitotic **spindle** by delaying anaphase onset. Evidence suggests that phosphorylations recognized by the 3F3/2 anti-phosphoepitope antibody may be involved in the kinetochore signaling of the **spindle checkpoint**. Mitotic cells lysed in detergent in the absence of phosphatase inhibitors rapidly lose expression of the 3F3/2 phosphoepitope. However, when ATP is added to lysed and rinsed mitotic cytoskeletons, kinetochores become rephosphorylated by an endogenous, bound kinase. Kinetochore rephosphorylation in vitro produced the same differential phosphorylation seen in appropriately fixed living cells. In chromosomes not yet aligned at the metaphase plate, kinetochores undergo rapid rephosphorylation, while those of fully congressed chromosomes are under-phosphorylated. However, latent 3F3/2 kinase activity is retained at

kinetochores of cells at all stages of mitosis including anaphase. This latent activity is revealed when rephosphorylation reactions are carried out for extended times. The endogenous, kinetochore-bound kinase can be chemically inactivated. Remarkably, a soluble kinase activity extracted from mitotic cells also caused differential rephosphorylation of kinetochores whose endogenous kinase had been chemically inactivated. We suggest that, in vivo, microtubule attachment alters the kinetochore 3F3/2 phosphoprotein, causing it to resist phosphorylation. This kinetochore modification is retained after cell lysis, producing a "memory" of the in vivo phosphorylation state.

L9 ANSWER 92 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:343797 BIOSIS
DN PREV200000343797
TI Infrequent mutation of the hBUB1 and hBUBR1 genes in human lung **cancer**.
AU Sato, Mitsuo; Sekido, Yoshitaka (1); Horio, Yoshitsugu; Takahashi, Masahide; Saito, Hidehiko; Minna, John D.; Shimokata, Kaoru; Hasegawa, Yoshinori
CS (1) Department of Clinical Preventive Medicine, Nagoya University School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, 466-8550 Japan
SO Japanese Journal of Cancer Research, (May, 2000) Vol. 91, No. 5, pp. 504-509. print.
ISSN: 0910-5050.
DT Article
LA English
SL English
AB Mitotic **checkpoint** defects of the cell cycle have been implicated in the development of human cancers. Since hBUB1 and hBUBR1, whose products function in the **spindle checkpoint** pathway, have been shown to be mutated in a subset of colon cancers with chromosomal instability, we investigated the contribution of these genes to lung **cancer** development. One hundred and two lung **cancer** (50 small cell lung cancers and 52 non-small cell lung cancers) and 4 mesothelioma cell line DNAs were analyzed by Southern blot analysis, but no rearrangements or deletions of hBUB1 and hBUBR1 were detected. Using single strand conformation polymorphism analysis, we studied all the 25 exons except exon 1 of the hBUB1 gene in 88 lung **cancer** DNAs. One lung **cancer** cell line, NCI-H345, showed a single nucleotide substitution, which resulted in an Arg-to-Gln change at codon 209 (CGA to CAA). Eleven cell line DNAs exhibited a single nucleotide polymorphism in intron 9 of hBUB1, all of which were heterozygous. Similar mutation analysis of hBUBR1 in 47 lung **cancer** cell line cDNAs revealed a frequent polymorphism at codon 349 (CAA to CGA) leading to a substitution of Gln to Arg but no mutations. Northern blot analyses showed that both hBUB1 and hBUBR1 genes were expressed in all of 31 lung **cancer** cell lines tested with no significant difference in the expression level. Our results suggest that alterations in hBUB1 and hBUBR1 rarely contributed to the genetic change of lung cancers.

L9 ANSWER 93 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:335696 BIOSIS
DN PREV200000335696
TI The role of p53 in the response to mitotic **spindle** damage.
AU Meek, D. W. (1)
CS (1) Biomedical Research Centre, Ninewells Hospital and Medical School, University of Dundee, Dundee, DD1 9SY UK
SO Pathologie Biologie, (Avril, 2000) Vol. 48, No. 3, pp. 246-254. print.
ISSN: 0369-8114.
DT General Review
LA English
SL English; French
AB The p53 **tumour** suppressor protein has defined roles in G1/S and

G2/M cell cycle checkpoints in response to a range of cellular stresses including DNA damage, dominant oncogene expression, hypoxia, metabolic changes and viral infection. In addition to these responses, p53 can also be activated when damage occurs to the mitotic **spindle**. Initially, **spindle** damage activates a p53-independent **checkpoint** which functions at the metaphase-anaphase transition and prevents cells from progressing through mitosis until the completion of **spindle** formation. Cells eventually escape from this block (a process termed 'mitotic slippage'), and an aberrant mitosis ensues in which sister chromatids fail to segregate properly. After a delay period, p53 responds to this mitotic failure by instituting a G1-like growth arrest, with an intact nucleus containing 4N DNA, but without the cells undergoing division. Cells lacking wild-type p53 are still able to arrest transiently at mitosis, and also fail to undergo division, underscoring that the delay in mitosis is p53-independent. However, these cells are not prevented from re-entering the cell cycle and can reduplicate their DNA unchecked, leading to polyploidy. Additionally, p53-null cells which experience **spindle** failure often show the appearance of micronuclei arising from poorly segregated chromosomes which have decondensed and been enclosed in a nuclear envelope. The ability of p53 to prevent their formation suggests an additional G2 involvement which prevents nuclear breakdown prior to mitosis. The molecular mechanism by which p53 is able to sense mitotic failure is still unknown, but may be linked to the ability of p53 to regulate duplication of the centrosome, the organelle which nucleates **spindle** formation.

L9 ANSWER 94 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:328359 BIOSIS
DN PREV200000328359
TI Alterations of cell cycle regulators in localized synovial sarcoma: A multifactorial study with prognostic implications.
AU Antonescu, Cristina R.; Leung, Denis H.; Dudas, Maria; Ladanyi, Marc; Brennan, Murray; Woodruff, James M.; Cordon-Cardo, Carlos (1)
CS (1) Department of Pathology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY, 10021 USA
SO American Journal of Pathology, (March, 2000) Vol. 156, No. 3, pp. 977-983. print.
ISSN: 0002-9440.
DT Article
LA English
SL English
AB Genetic alterations of cell cycle regulators are thought to represent uncommon and possible secondary events in sarcomas characterized by recurrent chromosomal translocations. The present study investigates this hypothesis on synovial sarcoma (SS), assessing the frequency of expression and possible clinical implications of detecting alterations in critical cell cycle regulatory proteins. A homogeneous cohort of 49 patients with localized SS, restricted to the extremity and with available long-term follow-up information, was selected from our files. We focused our study on molecules involved in the G1 **checkpoint** and G1-S transition, including cyclins D1 and E, p21WAF1, p27Kip1, mdm2, p53, and Ki67. A cutoff point of 10% immunoreactive **tumor** cell nuclei was selected to define a positive phenotype for any given marker, except for Ki67. High Ki67 proliferative index was considered when gtoreq20% **tumor** cells displayed nuclear immunoreactivity. Biphasic SS were analyzed, taking into account separately the expression of these proteins in the **spindle** and glandular components. Disease specific survival was modeled using the Kaplan-Meier method with log rank test and Cox regression. The cohort of patients analyzed included 23 females and 26 males, and the histological type distribution was 35 monophasic and 14 biphasic SS. The median follow-up for survivors was 53 months, with a 5-year disease-specific survival of 63% and a metastatic disease-free survival of 40%. The positive phenotypes identified for the different markers studied were as follows: cyclin D1, 59%; cyclin E, 29%; p21, 51%;

p27, 69%; mdm2, 59%; p53, 16%; and Ki67, 59%. We observed that positive p53, cyclin E, and high Ki67 proliferative index were correlated with survival, but only Ki67 and p53 were independent variables for prognostication. The present study suggests that alterations of cell cycle regulators are more common events in SS than originally thought. p53 overexpression could be of use as a marker together with a high Ki67 proliferative index, in identifying a subset of SS patients with incresed risk of **tumor** relapse.

L9 ANSWER 95 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:324481 BIOSIS
DN PREV200000324481
TI A human REV7 homolog that interacts with the polymerase zeta catalytic subunit hREV3 and the **spindle** assembly **checkpoint** protein hMAD2.
AU Murakumo, Yoshiki; Roth, Tim; Ishii, Hideshi; Rasio, Debora; Numata, Shin-ichiro; Croce, Carlo M.; Fishel, Richard (1)
CS (1) Genetics and Molecular Biology Program, Kimmel Cancer Center BLSB933, Thomas Jefferson University, 233 S. 10th St., Philadelphia, PA, 19107 USA
SO Journal of Biological Chemistry, (February 11, 2000) Vol. 275, No. 6, pp. 4391-4397. print.
ISSN: 0021-9258.
DT Article
LA English
SL English
AB Widespread alteration of the genomic DNA is a hallmark of tumors, and alteration of genes involved in DNA maintenance have been shown to contribute to the tumorigenic process. The DNA polymerase zeta of Saccharomyces cerevisiae is required for error-prone repair following DNA damage and consists of a complex between three proteins, scRev1, scRev3, and scRev7. Here we describe a candidate human homolog of S. cerevisiae Rev7 (hREV7), which was identified in a yeast two-hybrid screen using the human homolog of S. cerevisiae Rev3 (hREV3). The hREV7 gene product displays 23% identity and 53% similarity with scREV7, as well as 23% identity and 54% similarity with the human mitotic **checkpoint** protein hMAD2. hREV7 is located on human chromosome 1p36 in a region of high loss of heterozygosity in human tumors, although no alterations of hREV3 or hREV7 were found in primary human tumors or human **tumor** cell lines. The interaction domain between hREV3 and hREV7 was determined and suggests that hREV7 probably functions with hREV3 in the human DNA polymerase zeta complex. In addition, we have identified an interaction between hREV7 and hMAD2 but not hMAD1. While overexpression of hREV7 does not lead to cell cycle arrest, we entertain the possibility that it may act as an adapter between DNA repair and the **spindle** assembly **checkpoint**.

L9 ANSWER 96 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:285580 BIOSIS
DN PREV200000285580
TI Paclitaxel-induced cell death: Where the cell cycle and apoptosis come together.
AU Wang, Tzu-Hao; Wang, Hsin-Shih (1); Soong, Yung-Kwei
CS (1) Department of Obstetrics and Gynecology, Chang-Gung Memorial Hospital, Lin-Kou Medical Center, 5 Fu-Hsing Street, Kwei-Shan, Tao-Yuan, 333 Taiwan
SO Cancer, (June 1, 2000) Vol. 88, No. 11, pp. 2619-2628. print.
ISSN: 0008-543X.
DT General Review
LA English
SL English
AB BACKGROUND: Compelling evidence indicates that paclitaxel kills **cancer** cells through the induction of apoptosis. Paclitaxel binds microtubules and causes kinetic suppression (stabilization) of microtubule dynamics. The consequent arrest of the cell cycle at mitotic phase has been considered to be the cause of paclitaxel-induced cytotoxicity.

However, the biochemical events, downstream from paclitaxel's binding to microtubules, that lead to apoptosis are not well understood. METHODS: The authors examined recent scientific literature about the mechanisms by which paclitaxel exerts cytotoxicity. RESULTS: In addition to an arrest of the cell cycle at the mitotic phase in paclitaxel-treated cells, recent discoveries of activation of signaling molecules by paclitaxel and paclitaxel-induced transcriptional activation of various genes indicate that paclitaxel initiates apoptosis through multiple mechanisms. The **checkpoint** of mitotic **spindle** assembly, aberrant activation of cyclin-dependent kinases, and the c-Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK) are shown to be involved in paclitaxel-induced apoptosis. Consistent with observations that microtubules of different status (e.g., cytoskeletal microtubules vs. mitotic spindles) have different sensitivity to paclitaxel, the concentration of paclitaxel appears to be the major determinant of its apoptogenic mechanisms. CONCLUSIONS: Advances in research of the cell cycle and apoptosis have extended our understanding of the mechanisms of paclitaxel-induced cell death. Further elucidation of resistance and enhancement of paclitaxel-induced apoptosis should expedite the development of better paclitaxel-based regimens for **cancer** therapy.

L9 ANSWER 97 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:275301 BIOSIS
DN PREV200000275301
TI The human REV7 interacts with the polymerase zeta catalytic subunit hREV3 and the **spindle** assembly **checkpoint** protein hMAD2.
AU Murakumo, Yoshiki (1); Roth, T.; Ishii, H.; Rasio, D.; Numata, S.; Takahashi, M.; Croce, C. M.; Fishel, R.
CS (1) Nagoya Univ, Nagoya Japan
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2000) No. 41, pp. 714. print..
Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA April 01-05, 2000
ISSN: 0197-016X.
DT Conference
LA English
SL English

L9 ANSWER 98 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:268665 BIOSIS
DN PREV200000268665
TI The kinetochore-associated microtubule motor CENP-E is an essential component for establishing tension at kinetochores in gastric carcinoma cells.
AU Yao, Xuebiao (1); Ravikumar, T. S. (1)
CS (1) Albert Einstein Coll of Medicine, Bronx, NY USA
SO Gastroenterology, (April, 2000) Vol. 118, No. 4 Suppl. 2 Part 1, pp. AGA A857. print..
Meeting Info.: 101st Annual Meeting of the American Gastroenterological Association and the Digestive Disease Week. San Diego, California, USA May 21-24, 2000 American Gastroenterological Association
. ISSN: 0016-5085.
DT Conference
LA English
SL English

L9 ANSWER 99 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:248470 BIOSIS
DN PREV200000248470
TI Involvement of protein kinase C in taxol-induced polyploidization in a cultured sarcoma cell line.
AU Zong, Zhi-ping (1); Fujikawa-Yamamoto, Kohzaburo; Li, Ai-li; Yamaguchi, Nobuo; Chang, Yi-gang; Murakami, Manabu; Ishikawa, Yoshimaro

CS (1) Division of Basic Science, Medical Research Institute, Kanazawa Medical University, Uchinada, Ishikawa, 920-0293 Japan
SO European Journal of Pharmacology, (April 14, 2000) Vol. 394, No. 2-3, pp. 181-187.
ISSN: 0014-2999.
DT Article
LA English
SL English
AB Taxol was found to inhibit the proliferation and to induce the polyploidization of cultured methylcholanthrene-induced sarcoma cells (Meth-A cells). To investigate whether protein kinase C is involved in taxol-induced polyploidization, phorbol 12-myristate 13-acetate (PMA), which regulates the activity of protein kinase C, was used along with taxol to treat the cells. We found that PMA did not interfere with the proliferation and did not induce polyploidization by itself. However, at low concentration, taxol, which by itself did not induce polyploidization, clearly induced polyploidization in the presence of PMA. To explore the mechanism by which PMA potentiates polyploidization, the levels of the G1 **checkpoint**-related proteins cyclin E and cdk2, and those of the G2 **checkpoint**-related proteins cyclin B and cdc2 were determined by flow cytometry. We found that both G1 and G2 **checkpoint**-related proteins increased during the induction of polyploidization. To verify the relationship between protein kinase C and tubulin polymerization, flow cytometry was used to determine the total content of tubulin protein, and morphological observation was used to examine **spindle** organization. PMA did not affect the taxol-induced increase in tubulin protein, but markedly potentiated taxol-induced **spindle** disorganization. These findings suggest that protein kinase C plays an important role in regulating the induction of polyploidization in Meth-A cells.

L9 ANSWER 100 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:241662 BIOSIS
DN PREV200000241662
TI Differential **spindle** assembly **checkpoint** response in human lung adenocarcinoma cells.
AU Weitzel, Douglas H.; Vandre, Dale D. (1)
CS (1) Department of Physiology and Cell Biology, The Comprehensive Cancer Center, and The Molecular, Cellular, and Developmental Biology Program, The Ohio State University, 1645 Neil Ave., 302 Hamilton Hall, Columbus, OH, 43210 USA
SO Cell & Tissue Research, (April, 2000) Vol. 300, No. 1, pp. 57-65.
ISSN: 0302-766X.
DT Article
LA English
SL English
AB CI-980 is an antimicrotubule agent that binds the colchicine site on tubulin. We examined CI-980 cytotoxicity in two lung adenocarcinoma cell lines, A549 and A427. Depolymerization of microtubules following CI-980 treatment resulted in a mitotic arrest in the A549 population, but not in the A427 population. Similar responses were obtained following treatment with Taxol and nocodazole. Drug-treated A427 cells exited mitosis, generating a population dominated by multinucleated cells, while both multinucleated and apoptotic cells were present in the A549 population after extended drug treatment. CI-980-induced microtubule depolymerization was only partially reversible. However, regrowth of some microtubules in mitotic A549 cells following drug washout resulted in multinucleation of the population in the absence of apoptosis. These results show that A427 cells have a defective **spindle** assembly **checkpoint**. Levels of the MAD2 and BUB1 **checkpoint** proteins were similar in both A549 and A427 cells, suggesting that the **checkpoint** defect in the A427 cells is downstream of these proteins. In addition, induction of apoptosis in response to CI-980 correlates with the presence of a functional mitotic **checkpoint** and the extent of microtubule

depolymerization.

L9 ANSWER 101 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:188611 BIOSIS
DN PREV200000188611
TI Potential role of BRCA2 in a mitotic **checkpoint** after phosphorylation by hBUBR1.
AU Futamura, Manabu; Arakawa, Hirofumi; Matsuda, Koichi; Katagiri, Toyomasa; Saji, Shigetoyo; Miki, Yoshio; Nakamura, Yusuke (1)
CS (1) Human Genome Center, Institute of Medical Science, University of Tokyo, Shirokanedai, Minato-ku, Tokyo, 108-8639 Japan
SO Cancer Research, (March 15, 2000) Vol. 60, No. 6, pp. 1531-1535. ISSN: 0008-5472.
DT Article
LA English
SL English
AB BRCA2, a gene responsible for inherited susceptibility to breast **cancer** in a number of families, is thought to be critical for replication and repair of DNA during S-phase. To elucidate the physiological functions of BRCA2, we used a yeast two-hybrid system to screen for proteins that could associate with BRCA2. Here we report interaction of BRCA2 with a mitotic **checkpoint** protein, hBUBR1, and its phosphorylation by hBUBR1 in vitro. After cotransfection of BRCA2 and hBUBR1 expression vectors into the COS7 cell line, both proteins were stained together in the nuclei of cells whose **spindle** fibers were disrupted, but not in undamaged cells. Treatment with vincristine, which disrupts microtubules, significantly increased expression of both hBUBR1 and BRCA2 in the MCF7 cells. The results suggest that BRCA2 protein might be involved in a mitotic **checkpoint** in vivo after it has been phosphorylated by hBUBR1.

L9 ANSWER 102 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:128587 BIOSIS
DN PREV200000128587
TI Epstein-Barr virus EBNA3C can disrupt multiple cell cycle checkpoints and induce nuclear division divorced from cytokinesis.
AU Parker, Gillian A.; Touitou, Robert; Allday, Martin J. (1)
CS (1) Section of Virology and Cell Biology, Ludwig Institute for Cancer Research, Imperial College of Science, Technology and Medicine, St Mary's Campus, Norfolk Place, London, W2 1PG UK
SO Oncogene, (Feb. 3, 2000) Vol. 19, No. 5, pp. 700-709. ISSN: 0950-9232.
DT Article
LA English
SL English
AB Expression of EBNA3C is essential for the immortalization of B cells by EBV in vitro and, in co-operation with activated ras, EBNA3C has oncogenic activity in primary rodent fibroblasts. This suggested that this viral oncoprotein might disrupt the cyclin/CDK-pRb-E2F pathway, which regulates cell cycle progression at the restriction point (R-point) in G1 of the proliferation cycle. An assay was established in which transfected EBNA3C-positive cells could be sorted and simultaneously analysed for their distribution in the cell cycle. This revealed that in NIH3T3 fibroblasts compelled to arrest by serum-withdrawal, EBNA3C induces nuclear division that is often divorced from cytokinesis and so produces bi- and multinucleated cells. This was confirmed using the ecdysone-inducible system for expression of EBNA3C in human U2OS cells and by microinjection of expression vectors into NIH3T3 and U2OS. Further analysis revealed that in the inducible system, EBNA3C expression inhibits the accumulation of p27KIP1 but not the dephosphorylation of pRb. Experiments using the microtubule destabilizing drug nocodazole, showed that EBNA3C could abrogate the mitotic **spindle checkpoint**.

L9 ANSWER 103 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:96202 BIOSIS
DN PREV200000096202
TI Aurora/Ipl1p-related kinases, a new oncogenic family of mitotic serine-threonine kinases.
AU Giet, Regis; Prigent, Claude (1)
CS (1) Groupe Cycle Cellulaire, Faculte de Medecine, CNRS UPR411 Universite de Rennes I, 2 Avenue du Pr Leon Bernard, CS 34317, 35043, Rennes Cedex France
SO Journal of Cell Science, (Nov., 1999) Vol. 112, No. 21, pp. 3591-3601. ISSN: 0021-9533.
DT General Review
LA English
SL English
AB During the past five years, a growing number of serine-threonine kinases highly homologous to the Saccharomyces cerevisiae Ipl1p kinase have been isolated in various organisms. A Drosophila melanogaster homologue, aurora, was the first to be isolated from a multicellular organism. Since then, several related kinases have been found in mammalian cells. They localise to the mitotic apparatus: in the centrosome, at the poles of the bipolar **spindle** or in the midbody. The kinases are necessary for completion of mitotic events such as centrosome separation, bipolar **spindle** assembly and chromosome segregation. Extensive research is now focusing on these proteins because the three human homologues are overexpressed in various primary cancers. Furthermore, overexpression of one of these kinases transforms cells. Because of the myriad of kinases identified, we suggest a generic name: Aurora/Ipl1p-related kinase (AIRK). We denote AIRKs with a species prefix and a number, e.g. HsAIRK1.

L9 ANSWER 104 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:50232 BIOSIS
DN PREV200000050232
TI p53 does not control the **spindle** assembly cell cycle **checkpoint** but mediates G1 arrest in response to disruption of microtubule system.
AU Sablina, Anna A.; Agapova, Larissa S.; Chumakov, Peter M.; Kopnin, Boris P. (1)
CS (1) Laboratory of Cytogenetics, Cancer Research Center, Institute of Cancerogenesis, Kashirskoye shosse 24, Moscow, 115478 Russia
SO Cell Biology International, (1999) Vol. 23, No. 5, pp. 323-334. ISSN: 1065-6995.
DT Article
LA English
SL English
AB p53 plays a critical role as a **tumour**-suppressor in restricting the proliferation of damaged cells, thus preventing formation of genetically altered cell clones. Its inactivation leads, in particular, to accumulation of polyploid and aneuploid cells. To elucidate the role of p53 in control of chromosome number, we analysed its participation in the cell cycle checkpoints controlling: (1) **spindle** assembly; and (2) G1-to-S transitions in cells with disintegrated microtubule cytoskeleton. Treatment with 8-10 ng/ml of colcemid causing no visible destruction of the **spindle** leads to arrest of metaphase-to-anaphase transition in both p53-positive and p53-negative murine fibroblasts, as well as in p53-positive REF52 cells and their counterparts (where the p53 function was inactivated by transduction of dominant-negative p53 fragment). Furthermore, p53-positive and p53-defective rodent and human cells showed no significant difference in kinetics of metaphase-to-interphase transitions in cultures treated with high colcemid doses preventing **spindle** formation. These data argue against the hypothesis that p53 is a key component of the **spindle**-assembly **checkpoint**. However, p53 mediates activation of the G1 **checkpoint** in response to depolymerization of microtubules in interphase cells. Treatment of synchronized G0/G1 cells

with colcemid causes arrest of G1-to-S transition. Inactivation of the p53 function by transduction of dominant-negative p53 fragment abolishes the G1 **checkpoint** that prevents entry into S phase of cells with disrupted microtubules. Transduction of kinase-defective dominant-negative c-raf mutant or application of PD 098059, a specific inhibitor of MEK1, also abrogates the G1 cell cycle arrest in cells with disintegrated microtubule system. It seems that Raf-MAP-kinase signalling pathways are responsible for p53 activation induced by depolymerization of microtubules.

L9 ANSWER 105 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:42592 BIOSIS
DN PREV200000042592
TI P21waf1 is important for cyclin stabilization after **spindle** damage in human cells.
AU Mantel, C. (1); Braun, S. (1); Broxmeyer, H. E. (1)
CS (1) Dept. of Microbiology and Immunology, Walther Oncology Center, Indiana University School of Medicine, Indianapolis, IN USA
SO Blood, (Nov. 15, 1999) Vol. 94, No. 10 SUPPL. 1 PART 1, pp. 654a. Meeting Info.: Forty-first Annual Meeting of the American Society of Hematology New Orleans, Louisiana, USA December 3-7, 1999 The American Society of Hematology
. ISSN: 0006-4971.
DT Conference
LA English

L9 ANSWER 106 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:26850 BIOSIS
DN PREV200000026850
TI Evidence for an interaction of the metalloprotease-disintegrin **tumour** necrosis factor alpha convertase (TACE) with mitotic arrest deficient 2 (MAD2), and of the metalloprotease-disintegrin MDC9 with a novel MAD2-related protein, MAD2beta.
AU Nelson, Karen K.; Schlondorff, Johannes; Blobel, Carl P. (1)
CS (1) Cellular Biochemistry and Biophysics Program, Memorial Sloan-Kettering Cancer Center, Sloan-Kettering Institute, New York, NY, 10021 USA
SO Biochemical Journal, (Nov. 1, 1999) Vol. 343, No. 3, pp. 673-680. ISSN: 0264-6021.
DT Article
LA English
SL English
AB Metalloprotease-disintegrins are a family of transmembrane glycoproteins that have a role in fertilization, sperm migration, myoblast fusion, neural development and ectodomain shedding. In the present study we used the yeast two-hybrid system to search for proteins that interact with the cytoplasmic domain of two metalloprotease-disintegrins, **tumour** necrosis factor alpha convertase (TACE; ADAM17) and MDC9 (ADAM9; meltrin gamma). We have identified mitotic arrest deficient 2 (MAD2) as a binding partner of the TACE cytoplasmic domain, and a novel MAD2-related protein, MAD2beta, as a binding partner of the MDC9 cytoplasmic domain. MAD2beta has 23 % sequence identity with MAD2, which is a component of the **spindle** assembly (or mitotic) **checkpoint** mechanism.
Northern blot analysis of human tissues indicates that MAD2beta mRNA is expressed ubiquitously. The interaction of the TACE and MDC9 cytoplasmic domains with their binding partners has been confirmed biochemically. The independent identification ofMAD2 and MAD2beta as potential interacting partners of distinct metalloprotease-disintegrins raises the possibility of a link between metalloprotease-disintegrins and the cell cycle, or of functions for MAD2 and MAD2beta that are not related to cell cycle control.

L9 ANSWER 107 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1999:525132 BIOSIS
DN PREV199900525132

TI Signaling network of paclitaxel-induced apoptosis in the LNCaP prostate **cancer** cell line.
AU Panvichian, R.; Orth, K.; Pilat, M. J.; Day, M. L.; Day, K. C.; Yee, C.; Kamradt, J. M.; Pienta, K. J. (1)
CS (1) Department of Internal Medicine, University of Michigan Medical School, 1500 East Medical Center Drive, 7303 CCGC, Ann Arbor, MI, 48109-0946 USA
SO Urology, (Oct., 1999) Vol. 54, No. 4, pp. 746-752.
ISSN: 0090-4295.
DT Article
LA English
SL English
AB Objectives: To attempt to identify the relationship of the key regulator molecules in paclitaxel-induced apoptosis using two metastatic cell lines: the human prostate carcinoma LNCaP line and the cervical carcinoma HeLa cell line. Methods: Both LNCaP and HeLa cells were continuously exposed to clinically achievable concentrations of paclitaxel and observed for activation of programmed cell death as measured by cytotoxic dose-response curves, poly(adenosine diphosphate-ribose) polymerase cleavage, bcl-2 phosphorylation, and the activation of caspase-7 (interleukin-1 beta converting enzyme (ICE)-LAP3). Results: Initially, we asked whether paclitaxel-induced bcl-2 phosphorylation is triggered by the **spindle** assembly **checkpoint** via an active cdc2 kinase-dependent pathway and whether phosphorylation of endogenous bcl-2 is the signal that activates cell death machinery. Paclitaxel-induced G2/M cell cycle arrest correlated with cdc2 kinase activity and bcl-2 phosphorylation. Olomoucin, a specific inhibitor of cyclin-dependent kinases, inhibited bcl-2 phosphorylation. On the basis of these studies, we then investigated whether bcl-2 was phosphorylated in a cell cycle-dependent fashion. Analysis of synchronized HeLa cells demonstrated that endogenous bcl-2 is phosphorylated in a G2/M cell cycle-dependent manner without apoptosis. Conclusions: Our results indicate that the events associated with paclitaxel-induced cytotoxicity are connected to each other and represent the signaling network of paclitaxel-induced mitotic arrest and cell death. In addition, we confirmed that the death-decision of paclitaxel-induced apoptosis is not mediated by bcl-2 phosphorylation and believe that this decision may be mediated by the activated **spindle** assembly **checkpoint**.

L9 ANSWER 108 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1999:455605 BIOSIS
DN PREV199900455605
TI Mutational inactivation of mitotic **checkpoint** genes, hsMAD2 and hBUB1, is rare in sporadic digestive tract cancers.
AU Imai, Yasuo (1); Shiratori, Yasushi; Kato, Naoya; Inoue, Tohru; Omata, Masao
CS (1) Department of Gastroenterology, Faculty of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-8655 Japan
SO Japanese Journal of Cancer Research, (Aug., 1999) Vol. 90, No. 8, pp. 837-840.
ISSN: 0910-5050.
DT Article
LA English
SL English
AB Genetic instability is a key mechanism of tumorigenesis, and the instability exists at two distinct levels, the nucleotide and the chromosome levels. Disruption of the mitotic **spindle checkpoint** is one of the underlying mechanisms leading to aneuploidy and alterations of hsMAD2 and hBUB1, assumed to take part in the **spindle checkpoint** in human cells, have been found to be associated with chromosomal instability in some **tumor** cell lines. Therefore, we investigated the mutational status of the hsMAD2 and hBUB1 genes in 32 sporadic digestive tract cancers by reverse transcription-polymerase chain reaction-single strand conformation

polymorphism analysis. The entire coding sequence of the hsMAD2 gene, and conserved regions (codons 21-152 and codons 732-1043) presumed to be functionally important in the hBUB1 gene were analyzed. Mutation of the hsMAD2 gene was not observed at all and missense mutation of the hBUB1 gene was noted in one rectal **cancer** case. Sequencing analysis revealed an AGT-to-GGT missense mutation, substituting glycine for serine, at codon 950, which is conserved between budding yeast and human. These results indicate that mutations of the hsMAD2 and hBUB1 genes are very rare and presumably play a very restricted role in **tumor** development of sporadic cancers.

L9 ANSWER 109 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1999:441505 BIOSIS
DN PREV199900441505
TI Genomic analysis of **spindle checkpoint** gene hBUB1 in colorectal **cancer**.
AU Jaffrey, R. G. (1); Pritchard, S. C. (1); Clark, C. (1); Cassidy, J. (1); McLeod, H. L. (1)
CS (1) Oncology Group, Department of Medicine and Therapeutics, Univ. Aberdeen, Aberdeen, AB25 2ZD UK
SO British Journal of Cancer, (July, 1999) Vol. 80, No. SUPPL. 2, pp. 80. Meeting Info.: Joint Meeting of the British Association for Cancer Research, the British Oncological Association, the Association of Cancer Physicians and the Royal College of Radiologists Edinburgh, Scotland, UK July 11-14, 1999
ISSN: 0007-0920.
DT Conference
LA English

L9 ANSWER 110 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1999:431686 BIOSIS
DN PREV199900431686
TI Identification of frequent impairment of the mitotic **checkpoint** and molecular analysis of the mitotic **checkpoint** genes, hsMAD2 and p55CDC, in human lung cancers.
AU Takahashi, Takao; Haruki, Nobuhiro; Nomoto, Shuji; Masuda, Akira; Saji, Shigetoyo; Osada, Hirotaka; Takahashi, Takashi (1)
CS (1) Laboratory of Ultrastructure Research, Aichi Cancer Center Research Institute, 1-1 Kanokoden, Chikusa-ku, Nagoya, 464-8681 Japan
SO Oncogene, (July 29, 1999) Vol. 18, No. 30, pp. 4295-4300.
ISSN: 0950-9232.
DT Article
LA English
SL English
AB The mitotic **checkpoint** is thought to be essential for ensuring accurate chromosome segregation by implementing mitotic delay in response to a **spindle** defect. To date, however, very little data has become available on the defects of the mitotic **checkpoint** in human **cancer** cells. In the present study, impaired mitotic **checkpoint** was found in four (44%) of nine human lung **cancer** cell lines. To our knowledge, this is the first demonstration of frequent impairment of the mitotic **checkpoint** in this leading cause of **cancer** deaths. As an initial step towards elucidation of the underlying mechanism, we further undertook a search for mutations in a key component of the mitotic **checkpoint** , known as hsMAD2, and its immediate downstream molecule, p55CDC. No such mutations were found, however, in either 21 lung **cancer** cell lines or 25 primary lung **cancer** cases, although we could identify silent polymorphisms and the transcribed and processed hsMAD2 pseudogene that was subsequently mapped at 14q21-q23. The present observations appear to warrant further investigations, such as search for alterations in other components, to better understand the molecular pathogenesis of this fatal disease, and warn against potential misinterpretation when performing mutational analyses for other

cancer types based on cDNA templates.

L9 ANSWER 111 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1999:423297 BIOSIS
DN PREV199900423297
TI Mitotic **checkpoint** inactivation fosters transformation in cells lacking the breast **cancer** susceptibility gene, Brca2.
AU Lee, Hyunsook; Trainer, Alison H.; Friedman, Lori S.; Thistlethwaite, Fiona C.; Evans, Martin J.; Ponder, Bruce A. J.; Venkitaraman, Ashok R. (1)
CS (1) Medical Research Council Laboratory of Molecular Biology, Hills Road, Cambridge, CB2 2QH UK
SO Molecular Cell, (July, 1999) Vol. 4, No. 1, pp. 1-10. ISSN: 1097-2765.
DT Article
LA English
SL English
AB The murine Brca2 gene encodes a nuclear protein implicated in DNA repair. Brca2 behaves as a **tumor** suppressor, but paradoxically, its truncation causes proliferative arrest and spontaneous chromosomal damage. Here, we report that inactivation of cell cycle checkpoints responsive to mitotic **spindle** disruption, by mutant forms of p53 or Bub1, relieves growth arrest and initiates neoplastic transformation in primary cells homozygous for truncated Brca2. Tumors from Brca2-deficient animals exhibit dysfunction of the **spindle** assembly **checkpoint**, accompanied by mutations in p53, Bub1, and Mad3L. The chromosomal aberrations precipitated by Brca2 truncation can be suppressed by mutant forms of Bub1 and p53. Thus, inactivating mutations in mitotic **checkpoint** genes likely cooperate with BRCA2 deficiency in the pathogenesis of inherited breast **cancer**, with important implications for treatment.

L9 ANSWER 112 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1999:378082 BIOSIS
DN PREV199900378082
TI Taxol suppresses dynamics of individual microtubules in living human **tumor** cells.
AU Yvon, Anne-Marie C.; Wadsworth, Patricia; Jordan, Mary Ann (1)
CS (1) Department of Molecular, Cellular, and Developmental Biology, University of California, Santa Barbara, CA, 93106 USA
SO Molecular Biology of the Cell, (April, 1999) Vol. 10, No. 4, pp. 947-959. ISSN: 1059-1524.
DT Article
LA English
SL English
AB Microtubules are intrinsically dynamic polymers, and their dynamics play a crucial role in mitotic **spindle** assembly, the mitotic **checkpoint**, and chromosome movement. We hypothesized that, in living cells, suppression of microtubule dynamics is responsible for the ability of taxol to inhibit mitotic progression and cell proliferation. Using quantitative fluorescence video microscopy, we examined the effects of taxol (30-100 nM) on the dynamics of individual microtubules in two living human **tumor** cell lines: Caov-3 ovarian adenocarcinoma cells and A-498 kidney carcinoma cells. Taxol accumulated more in Caov-3 cells than in A-498 cells. At equivalent intracellular taxol concentrations, dynamic instability was inhibited similarly in the two cell lines. Microtubule shortening rates were inhibited in Caov-3 cells and in A-498 cells by 32 and 26%, growing rates were inhibited by 24 and 18%, and dynamicity was inhibited by 31 and 63%, respectively. All mitotic spindles were abnormal, and manyinterphase cells became multinucleate (Caov-3, 30%; A-498, 58%). Taxol blocked cell cycle progress at the metaphase/anaphase transition and inhibited cell proliferation. The results indicate that suppression of microtubule dynamics by taxol deleteriously affects the ability of **cancer** cells to properly

assemble a mitotic **spindle**, pass the metaphase/anaphase **checkpoint**, and produce progeny.

L9 ANSWER 113 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1999:339515 BIOSIS
DN PREV199900339515
TI The **cancer** antiapoptosis mouse survivin gene: Characterization of locus and transcriptional requirements of basal and cell cycle-dependent expression.
AU Li, Fengzhi; Altieri, Dario C. (1)
CS (1) Boyer Center for Molecular Medicine 436B, Yale University School of Medicine, 295 Congress Avenue, New Haven, CT, 06536 USA
SO Cancer Research, (July 1, 1999) Vol. 59, No. 13, pp. 3143-3151. ISSN: 0008-5472.
DT Article
LA English
SL English
AB Survivin is the first apoptosis inhibitor described to date to be expressed in G2-M in a cell cycle-dependent manner and to directly associate with mitotic **spindle** microtubules. To gain additional insights into this novel apoptotic **checkpoint**, we have now characterized the mouse survivin locus. Hybridization screening of mouse BAC libraries identified a survivin gene containing four exons and three introns, spanning >50 kb on the telomere of chromosome 11E2 and generating a 0.85-kb mRNA versus the 1.9-kb human transcript. A mouse survivin protein of 140 amino acids (Mrapprx16,200) was 84% identical to its human orthologue and contained a structurally unique single baculovirus iap repeat (BIR) and a -COOH-terminus coiled domain instead of a RING finger. Analysis of the 5'-flanking region of the mouse survivin gene revealed a TATA-less promoter containing a canonical CpG island, numerous Sp1 sites, two cell cycle-dependent elements (CDEs), and one cell cycle gene homology region (CHR), typically found in G2-M-expressed genes. Primer extension and S1 nuclease mapping identified three transcription start sites at position -32, -36, and -40 from the initiating ATG. Transfection of survivin promoter-luciferase constructs identified a minimal promoter region within the most proximal 174 bp upstream of the first ATG. Mutagenesis of the CDE/CHR elements and Sp1 sites in this region, alone or in combination, reduced transcriptional activity by 40-60% in asynchronously growing cells and abolished cell cycle periodicity in G2-M-synchronized cells. These data demonstrate that cell cycle expression of survivin requires integration of typical CDE/CHR G1 repressor elements and basal transcriptional activity by Sp1. Disruption of these transcriptional requirements may provide an alternative strategy to block the overexpression of survivin in **cancer**.

L9 ANSWER 114 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1999:311122 BIOSIS
DN PREV199900311122
TI Mutation analysis of hBUB1 in aneuploid HNSCC and lung **cancer** cell lines.
AU Yamaguchi, Kengo; Okami, Kenji; Hibi, Kenji; Wehage, Scott L.; Jen, Jin; Sidransky, David (1)
CS (1) Division of Head and Neck Cancer Research, Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins University, 720 Rutland Avenue, 818 Ross Research Building, Baltimore, MD, 21205-2196 USA
SO Cancer Letters, (May 24, 1999) Vol. 139, No. 2, pp. 183-187. ISSN: 0304-3835.
DT Article
LA English
SL English
AB Aneuploidy is frequently observed in many types of human **cancer** cells, suggesting that mutations of genes required for chromosomal stability may occur in human tumors. The BUB gene is a component of the mitotic **checkpoint** in budding yeast that delays anaphase in the

presence of **spindle** damage thus increasing the probability of successful delivery of a euploid genome to each daughter cell. Recently, human homologues of the BUB gene were identified and mutant alleles of hBUB1 were detected in two colorectal **tumor** cell lines. Transfection of one mutant allele led to dominant disruption of the mitotic **checkpoint** control in a euploid cell, suggesting that aneuploidy in some tumors could be due to defects in the mitotic **checkpoint**. We analyzed the entire coding sequence of hBUB1 for mutation in 31 head and neck squamous cell carcinoma (HNSCC) and lung **cancer** cell lines, most with severe aneuploidy. We found expression of the hBUB1 gene in all cell lines and only a single nucleotide substitution in one cell line without a resultant change in amino acid sequence. Our study demonstrates that hBUB1 is rarely a target for genetic alterations in tumors of the respiratory tract.

L9 ANSWER 115 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1999:308530 BIOSIS
DN PREV199900308530
TI Defective control of apoptosis and mitotic **spindle** **checkpoint** in heterozygous carriers of ATM mutations.
AU Shigeta, Teruko; Takagi, Masatoshi; Delia, Domenico; Chessa, Luciana; Iwata, Satoshi; Kanke, Yusuke; Asada, Minoru; Eguchi, Mariko; Mizutani, Shuki (1)
CS (1) Department of Virology, The National Children's Medical Research Center, 3-35-31, Taishido, Setagaya-ku, Tokyo, 154 Japan
SO Cancer Research, (June 1, 1999) Vol. 59, No. 11, pp. 2602-2607. ISSN: 0008-5472.
DT Article
LA English
SL English
AB Ataxia telangiectasia (AT) carrier-derived lymphoblastoid cell lines (AT-LCLs/hetero) with suboptimal ATM protein expression were examined for the regulation of radiosensitivity, apoptosis, and mitotic **spindle** **checkpoint** in response to DNA-damaging agents. Although AT-LCLs/hetero showed intermediate radiation sensitivity, as determined by clonogenic assay, they were resistant to early-onset apoptosis, as much as AT patient-derived LCLs (AT-LCLs/homo). Furthermore, two of three AT-LCLs/hetero showed defective mitotic **spindle** **checkpoint** control in response to X-ray irradiation, which is a recently characterized biological feature in AT-LCLs/homo. Our findings indicate that carriers of ATM mutation have biological abnormalities due to haploinsufficiency of ATM protein or dominant-negative effect of mutant ATM protein. Thus, although it is still controversial whether ATM mutation carriers are at higher risk for **cancer** during adulthood, our findings based on in vitro biological indicatorssupport the notion that at least some of such carriers are at a higher risk for **cancer** development than those without ATM mutation. Our findings may help to reevaluate epidemiological studies on **cancer** susceptibility in AT carriers.

L9 ANSWER 116 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1999:287981 BIOSIS
DN PREV199900287981
TI CENP-E interacts with BubR1 and participates in **spindle** assembly **checkpoint** signaling in human gastric carcinoma cells.
AU Yao, Xuebiao (1); Zheng, Y.
CS (1) Univ of Wisconsin, Madison, WI USA
SO Gastroenterology, (April, 1999) Vol. 116, No. 4 PART 2, pp. A533. Meeting Info.: Digestive Disease Week and the 100th Annual Meeting of the American Gastroenterological Association Orlando, Florida, USA May 16-19, 1999 American Gastroenterological Association . ISSN: 0016-5085.
DT Conference
LA English

L9 ANSWER 117 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1999:195196 BIOSIS
DN PREV199900195196
TI A Gln/Arg polymorphism at codon 349 of the hBUBR1 gene.
AU Katagiri, Toyomasa (1); Futamura, Manabu; Nakamura, Yusuke
CS (1) Laboratory of Molecular Medicine, Human Genome Center, Institute of Medical Science, University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo, 108-8639 Japan
SO Journal of Human Genetics, (1999) Vol. 44, No. 2, pp. 131-132. ISSN: 1434-5161.
DT Article
LA English
AB We found a glutamine/arginine polymorphism at codon 349 of the hBUBR1 gene, encoding a protein kinase required for **spindle** assembly **checkpoint** function. The observed heterozygosity was estimated to be 45% in the Japanese population. This polymorphism may be helpful for genetic studies of many **cancer** types in which chromosomal instability is observed.

L9 ANSWER 118 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1999:112126 BIOSIS
DN PREV199900112126
TI Negative control elements of the cell cycle in human tumors.
AU Adams, Peter D. (1); Kaelin, William G., Jr.
CS (1) Fox Chase Cancer Center, 7701 Burholme Avenue, Philadelphia, PA 19104 USA
SO Current Opinion in Cell Biology, (Dec., 1998) Vol. 10, No. 6, pp. 791-797. ISSN: 0955-0674.
DT General Review
LA English

L9 ANSWER 119 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1999:35904 BIOSIS
DN PREV199900035904
TI Prevention of mammalian DNA reduplication, following the release from the mitotic **spindle checkpoint**, requires p53 protein, but not p53-mediated transcriptional activity.
AU Notterman, D.; Young, S.; Wainger, B.; Levine, A. J. (1)
CS (1) Dep. Mol. Biol., Princeton Univ., Princeton, NJ 08544 USA
SO Oncogene, (Nov. 26, 1998) Vol. 17, No. 21, pp. 2743-2751. ISSN: 0950-9232.
DT Article
LA English
AB The **tumor** suppressor p53 has been identified as a component of a mitotic **spindle checkpoint**. When exposed to a **spindle**-disrupting drug such as nocodazole, fibroblasts derived from mice having wild-type p53 are blocked with a 4N content of DNA. Conversely, fibroblasts from p53-deficient mice become polyploid. To learn if transcriptional activation of downstream genes by p53 plays a role in this putative **checkpoint**, three cell lines were exposed to nocodazole. In one line, p53 protein is not expressed, while the other two cell lines over-express p53. In one of these two lines, the N-terminal transactivation domain is wild-type and in the second, this region contains a mutation that eliminates the ability of the protein to act as a transcription factor. Incubation with nocodazole of cells containing wild-type p53 results in accumulation of both 2N and 4N populations of cells. Under the same conditions, cells containing a transactivation-deficient mutant of p53 accumulate a 4N population of cells, but not a 2N population of cells. Cells entirely deficient in p53 protein become hyperdiploid, and display 8N to 16N DNA content. In all three cell lines, nocodazole elicited an initial increase in mitotic cells, but within 24 h the mitotic index returned to baseline. Expression patterns of cyclins B and D indicated that following entry into mitosis, the cells returned to a

G1 state but with 4N DNA content. Subsequent re-duplication of DNA beyond 4N is prevented in cells containing either wild-type or transcriptionally inactive p53 protein. In cells entirely lacking p53 protein, DNA is re-duplicated (without an intervening mitosis) and the cells become hyperdiploid. These experiments indicate that p53 does not participate in the transient mitotic arrest that follows **spindle** disruption, but is essential to prevent subsequent reduplication of DNA and the resulting hyperdiploid state. This function is intact in a mutant that is transcriptionally inactive.

L9 ANSWER 120 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1999:27863 BIOSIS
DN PREV199900027863
TI Control of apoptosis and mitotic **spindle checkpoint** by survivin.
AU Li, Fengzhi; Ambrosini, Grazia; Chu, Emily Y.; Plescia, Janet; Tognin, Simona; Marchisio, Pier Carlo; Altieri, Dario C. (1)
CS (1) Boyer Cent. Mol. Med., Dep. Pathol., Yale Univ. Sch. Med., 295 Congress Ave., New Haven, CT 06536 USA
SO Nature (London), (Dec. 10, 1998) Vol. 396, No. 6711, pp. 580-584. ISSN: 0028-0836.
DT Article
LA English
AB Progression of the cell cycle and control of apoptosis (programmed cell death) are thought to be intimately linked processes, acting to preserve homeostasis and developmental morphogenesis. Although proteins that regulate apoptosis have been implicated in restraining cell-cycle entry and controlling ploidy (chromosome number), the effector molecules at the interface between cell proliferation and cell survival have remained elusive. Here we show that a new inhibitor of apoptosis (IAP) protein, survivin, is expressed in the G2/M phase of the cell cycle in a cycle-regulated manner. At the beginning of mitosis, survivin associates with microtubules of the mitotic **spindle** in a specific and saturable reaction that is regulated by microtubule dynamics. Disruption of survivin-microtubule interactions results in loss of survivin's anti-apoptosis function and increased caspase-3 activity, a mechanism involved in cell death, during mitosis. These results indicate that survivin may counteract a default induction of apoptosis in G2/M phase. The overexpression of survivin in **cancer** may overcome this apoptotic **checkpoint** and favour aberrant progression of transformed cells through mitosis.

L9 ANSWER 121 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1998:513179 BIOSIS
DN PREV199800513179
TI Defective control of apoptosis, radiosensitivity, and **spindle checkpoint** in ataxia telangiectasia.
AU Takagi, Masatoshi; Delia, Domenico; Chessa, Luciana; Iwata, Satoshi; Shigeta, Teruko; Kanke, Yusuke; Goi, Kumiko; Asada, Minoru; Eguchi, Mariko; Kodama, Chie; Mizutani, Shuki (1)
CS (1) Dep. Virol., Natl. Child. Med. Res. Cent., 3-35-31 Taishido, Setagaya-ku, Tokyo 154 Japan
SO Cancer Research, (Nov. 1, 1998) Vol. 58, No. 21, pp. 4923-4929. ISSN: 0008-5472.
DT Article
LA English
AB We examined the regulation of apoptosis, radiosensitivity, and **spindle checkpoint** in response to DNA-damaging agents in ataxia telangiectasia (AT)-derived lymphoblastoid cell lines (AT-LCLs), which lack AT mutated (ATM) protein expression. In addition to the previous findings that AT-LCLs are defective in regulation of cell cycle at the G1, S, and G2-M checkpoints in response to X-ray irradiation (X-IR) and are highly sensitive to X-IR (J. Biol. Chem., 271: 20486-20493,1996), we showed for the first time that AT-LCLs were defective in

X-IR-associated **spindle checkpoint** control. The cells were also resistant to early apoptosis as much as LCLs derived from patients with Li-Fraumeni syndrome (LFS-LCLs). Terminal deoxynucleotidyl transferase-mediated nick end labeling assay of LCLs, however, demonstrated a significant increase in apoptotic cells among AT-LCLs cultured over a longer period after X-IR. These findings were in contrast to those of LFS-LCL, which showed very little increase in terminal deoxynucleotidyl transferase-mediated nick end labeling-positive population, even in cells with hyperploidy. Thus, although early apoptosis and cell cycle controls in response to DNA damage are disrupted in both ATM and p53 mutations, cells from AT patients are much more susceptible to late-onset apoptosis than those of LFS. These differences may depend on the level of accumulation of DNA damage and/or threshold that triggers late-onset cell death in ATM or p53 mutations. Our findings allow a better understanding of the role of ATM in p53-dependent and independent signal transduction pathways in response to DNA damaging agents.

L9 ANSWER 122 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1998:498063 BIOSIS
DN PREV199800498063
TI Human Bub1: A putative **spindle checkpoint** kinase closely linked to cell proliferation.
AU Ouyang, Bin; Lan, Zhengdao; Meadows, Juliana; Pan, Huiqi; Fukasawa, Kenji; Li, Wenqing; Dai, Wei (1)
CS (1) Div. Hematol.-Oncol., Univ. Cincinnati Coll. Med., K-Pavilion, ML-508, 231 Bethesda Ave., Cincinnati, OH 45267 USA
SO Cell Growth & Differentiation, (Oct., 1998) Vol. 9, No. 10, pp. 877-885. ISSN: 1044-9523.
DT Article
LA English
AB Eukaryotic cells have evolved a mechanism that delays the onset of anaphase until chromosomes are properly positioned on the **spindle** . To understand the molecular basis of such surveillance mechanism in human cells, we have cloned a full-length cDNA encoding a putative comparison reveals that hhBub1 is a structurally identity with BUB1 of budding yeast. In addition, the NH2-terminal portion (161 amino acids) of hBub1 shows known to be involved in the mitotic **checkpoint** response pathway. Northern blot analyses show that the hBub1 mRNA level is abundantly expressed in tissues or cells with a high mitotic index. When Dami cells undergo terminal differentiation after treatment with phorbol ester, hBub1 expression in this cell line is down-regulated rapidly. The hBub1 protein level is low in G1 and remains relatively constant in S, G2, and M phases. Immunofluorescence analysis shows that hBub1 protein colocalizes with a centromere kinetochore antigen CREST in interphase, mitotic prophase, and nocodazole-treated cells. Antibody electroporation experiments show that hBub1 is an important component of the **spindle checkpoint** pathway. Furthermore, fluorescence in situ hybridization analysis maps the hBub1 gene to chromosome 2q12-13. Our studies suggest that hBub1 expression is restricted to proliferating cells and appears to be involved in regulating cell cycle facilitate the study of its role in **spindle checkpoint** control as well as its potential role in certain genetic disorders.

L9 ANSWER 123 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1998:321455 BIOSIS
DN PREV199800321455
TI PD 98059 prevents establishment of the **spindle** assembly **checkpoint** and inhibits the G2-M transition in meiotic but not mitotic cell cycles in Xenopus.
AU Cross, Darren A. E.; Smythe, Carl (1)
CS (1) MRC Protein Phosphorylation Unit, Dep. Biochem., Med. Sci. Inst., Univ. Dundee, Dundee DD1 4HN UK
SO Experimental Cell Research, (May 25, 1998) Vol. 241, No. 1, pp. 12-22. ISSN: 0014-4827.

DT Article
LA English
AB Most chemotherapeutic agents block DNA replication, damage DNA, or interfere with chromosome segregation. The existence of checkpoints, which monitor these events, indicates that mechanisms exist to avoid death when essential cellular events are inhibited. A molecular understanding of cellular checkpoints should therefore provide opportunities for the development of inhibitors of **checkpoint** controls which may increase the potency of chemotherapeutic drugs by inducing catastrophic cell cycle progression. The molecular dissection of cell cycle arrest points is facilitated in the Xenopus egg/oocyte system, in which cell-free systems retain both S/M and **spindle** assembly checkpoints.
Members of the MAP kinase family have been shown to play a role in the induction of G2 to M transition during oocyte maturation and have been implicated in the maintenance of either cytostatic factor- or **spindle** assembly **checkpoint**-induced M-phase arrest.
Here, we have examined the effects of the inhibitor of MAP kinase kinase activation, PD 98059, on cell cycle progression in Xenopus oocytes and in cell-free extracts. This inhibitor is highly specific for the kinase which activates the classical p42/p44 MAP kinase, having no effect on upstream activators of stress-activated protein kinases. We have found that PD 98059 inhibits oocyte maturation, consistent with a role for p42 MAP kinase as a rate-limiting component in the induction of meiosis, but had no effect on the timing of G2-M transition in cell-free extracts indicating that, unlike meiosis, p42 MAP kinase activation is not limiting for normal mitotic M phase entry. However, we found that cytostatic factor-induced metaphase arrest, as well as the **spindle** assembly **checkpoint**, were both abolished in the presence of the drug. These results demonstrate that p42 MAP kinase, and not some other member of the MAP kinase family, is responsible for both CSF- and **checkpoint** -induced metaphase arrest and suggest that PD 98059 and similar agents may have considerable therapeutic potential for the potentiation of chemotherapeutic regimes.

L9 ANSWER 124 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1998:299305 BIOSIS
DN PREV199800299305
TI A cytokinesis **checkpoint** requiring the yeast homologue of an APC-binding protein.
AU Muhua, Li; Adames, Neil R.; Murphy, Michael D.; Shields, Colleen R.; Cooper, John A. (1)
CS (1) Dep. Cell Biol. and Physiol., Washington Univ. Sch. Med., St. Louis, MO 63110 USA
SO Nature (London), (June 4, 1998) Vol. 393, No. 6684, pp. 487-491. ISSN: 0028-0836.
DT Article
LA English
AB **Checkpoint** controls ensure that events of the cell-division cycle are completed with fidelity and in the correct order. In budding yeast with a mutation in the motor protein dynein, the mitotic **spindle** is often misaligned and therefore slow to enter the neck between mother cell and budding daughter cell. When this occurs, cytokinesis (division of the cytoplasm into two) is delayed until the **spindle** is properly positioned. Here we describe mutations that abolish this delay, indicating the existence of a new **checkpoint** mechanism. One mutation lies in the gene encoding the yeast homologue of EB1, a human protein that binds the adenomatous polyposis coli (APC) protein, a **tumour** suppressor. EB1 is located on microtubules of the mitotic **spindle** and is important in **spindle** assembly. EB1 may therefore, by associating with microtubules, contribute to the sensor mechanism that activates the **checkpoint**. Another mutation affects Stt4, a phosphatidylinositol-4-OH kinase. Cold temperature is an environmental stimulus that causes misalignment of the mitotic **spindle** in yeast and appears to activate this

checkpoint mechanism.

L9 ANSWER 125 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1998:273535 BIOSIS
DN PREV199800273535
TI An oncogenic form of p53 confers a dominant, gain-of-function phenotype that disrupts **spindle checkpoint** control.
AU Gualberto, Antonio; Aldape, Kenneth; Kozakiewicz, Krystyna; Tlsty, Thea D. (1)
CS (1) Dep. Pathol., 513 Parnassus Ave., P.O. Box 0506, HSW 451, Univ. California San Francisco Sch. Med., San Francisco, CA 94143-0506 USA
SO Proceedings of the National Academy of Sciences of the United States of America, (April 28, 1998) Vol. 95, No. 9, pp. 5166-5171. ISSN: 0027-8424.
DT Article
LA English
AB Although it is well-established that p53 functions as a **tumor** suppressor gene, certain mutations exhibit gain-of-function activities that increase oncogenic transformation. We have found a common class of p53 missense mutation that exhibits a dominant, gain-of-function activity that generates genomic instability. Fibroblasts from Li-Fraumeni syndrome heterozygotes with such mutations generate polyploid cells when exposed to **spindle** depolymerizing agents. Expression of such mutant alleles in normal fibroblasts yields the same phenotype. This class of dominant, gain-of-function p53 mutation (p53RSC, relaxed **spindle** check-point allele) does not require the transcriptional activation function of p53 for this behavior. Thus p53 mutations can contribute to progression of a **cancer** cell not only by absence of p53 **tumor** suppressor activity but also by the presence of an activity that promotes genetic instability.

L9 ANSWER 126 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1998:230311 BIOSIS
DN PREV199800230311
TI Chromosomal instability is correlated with telomere erosion and inactivation of G2 **checkpoint** function in human fibroblasts expressing human papillomavirus type 16 E6 oncoprotein.
AU Filatov, Leonid; Golubovskaya, Vita; Hurt, John C.; Byrd, Laura L.; Phillips, Jonathan M.; Kaufmann, William K. (1)
CS (1) Dep. Pathol. Lab. Med., Lineberger Comprehensive Cancer Cent., Univ. North Carolina Chapel Hill, Chapel Hill, NC 27599-7295 USA
SO Oncogene, (April 9, 1998) Vol. 16, No. 14, pp. 1825-1838. ISSN: 0950-9232.
DT Article
LA English
AB Cell cycle checkpoints and **tumor** suppressor gene functions appear to be required for the maintenance of a stable genome in proliferating cells. In this study chromosomal destabilization was monitored in relation to telomere structure, lifespan control and G2 **checkpoint** function. Replicative senescence was inactivated in secondary cultures of human skin fibroblasts by expressing the human papillomavirus type 16 (HPV-16) E6 oncoprotein to inactivate p53. Chromosome aberrations were enumerated during in vitro aging of isogenic control (F5neo) and HPV16E6-expressing (F5E6) fibroblasts. We found that structural and numerical aberrations in chromosomes were significantly increased in F5E6 cells during aging in vitro and fluorescence in situ hybridization (FISH) analysis using chromosome-specific probes demonstrated the occurrence of rearrangements involving chromosome 4 and 6 in genetically unstable F5E6 cells. Flow cytometry and karyotypic analyses revealed increased polyploidy and aneuploidy in F5E6 cells only at passages > 16, although these cells displayed defective mitotic **spindle checkpoint** function associated with inactivation of p53 at passages 5 and 16. G2 **checkpoint** function was confirmed to be gradually but progressively inactivated during in vitro

aging of E6-expressing cells. Aging of F5neo fibroblasts was documented during in vitro passaging by induction of a senescence-associated marker, pH 6.0 lysosomal beta-galactosidase. F5E6 cells displayed extension of in vitro lifespan and did not induce beta-galactosidase at high passage. Erosion of telomeres during in vitro aging of telomerase-negative F5neo cells was demonstrated by Southern hybridization and by quantitative FISH analysis on an individual cell level. Telomeric signals diminished continuously as F5neo cells aged in vitro being reduced by 80% near the time of replicative senescence. Telomeric signals detected by FISH also decreased continuously during aging of telomerase-negative F5E6 cells, but telomeres appeared to be stabilized at passage 34 when telomerase was expressed. Chromosomal instability in E6-expressing cells was correlated ($P<0.05$) with both loss of telomeric signals and inactivation of G2 **checkpoint** function. The results suggest that chromosomal stability depends upon a complex interaction among the systems of telomere length maintenance and cell cycle checkpoints.

L9 ANSWER 127 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1998:224576 BIOSIS
DN PREV199800224576
TI Localization of motor-related proteins and associated complexes to active, but not inactive, centromeres.
AU Faulkner, Nicole E.; Vig, Baldev; Echeverri, Christophe J.; Wordeman, Linda; Vallee, Richard B. (1)
CS (1) Cell Biol. Group, Worcester Foundation Biomed. Res., Shrewsbury, MA 01545 USA
SO Human Molecular Genetics, (April, 1998) Vol. 7, No. 4, pp. 671-677. ISSN: 0964-6906.
DT Article
LA English
AB Multicentric chromosomes are often found in **tumor** cells and certain cell lines. How they are generated is not fully understood, though their stability suggests that they are non-functional during chromosome segregation. Growing evidence has implicated microtubule motor proteins in attachment of chromosomes to the mitotic **spindle** and in chromosome movement. To better understand the molecular basis for the inactivity of centromeres associated with secondary constrictions, we have tested these structures by immunofluorescence microscopy for the presence of motor complexes and associated proteins. We find strong immunoreactivity at the active, but not inactive, centromeres of prometaphase multicentric chromosomes using antibodies to the cytoplasmic dynein intermediate chains, three components of the dynactin complex (dynamitin, Arp1 and p150Glued), the kinesin-related proteins CENP-E and MCAK and the proposed structural and **checkpoint** proteins HZW10, CENP-F and Mad2p. These results offer new insight into the assembly and composition of both primary and secondary constrictions and provide a molecular basis for the apparent inactivity of the latter during chromosome segregation.

L9 ANSWER 128 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1998:118292 BIOSIS
DN PREV199800118292
TI p53 and pRb prevent rereplication in response to microtubule inhibitors by mediating a reversible G1 arrest.
AU Khan, Shireen Hussain; Wahl, Geoffrey M. (1)
CS (1) Gene Expression Lab., Salk Inst., Univ. Calif. at San Diego, La Jolla, CA 92037 USA
SO Cancer Research, (Feb. 1, 1998) Vol. 58, No. 3, pp. 396-401. ISSN: 0008-5472.
DT Article
LA English
AB Cell cycle checkpoints are safeguards that ensure the initiation of downstream events only after completion of upstream processes. The **tumor** suppressors p53 and pRb prevent initiation of a second round

of replication in response to **spindle** inhibitors, but it has yet to be proven that this is a mitotic **checkpoint** response. We show that asynchronous human fibroblasts arrest in G1 with 4 N DNA content after nocodazole treatment, whereas isogenic p53- and pRb-deficient fibroblasts re-replicate. Importantly, nocodazole elicits a reversible arrest in G0-G1 synchronized normal human fibroblasts but not in isogenic p53-deficient derivatives. Furthermore, the G1 cyclin-dependent kinase inhibitors p21 and p16 also play critical roles in limiting re-replication. Hence, p53 and pRb are required during G1 to prevent entry into a replicative cycle and appear to provide a connection between the structural integrity of the microtubules and the cell cycle machinery in interphase cells.

L9 ANSWER 129 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1998:118126 BIOSIS
DN PREV199800118126
TI Characterization of the p53-dependent postmitotic **checkpoint** following **spindle** disruption.
AU Lanni, Jennifer S.; Jacks, Tyler (1)
CS (1) MIT Cent. Cancer Res., 40 Ames St., Build. E17-517, Cambridge, MA 02139 USA
SO Molecular and Cellular Biology, (Feb., 1998) Vol. 18, No. 2, pp. 1055-1064.
ISSN: 0270-7306.
DT Article
LA English
AB The p53 **tumor** suppressor gene product is known to act as part of a cell cycle **checkpoint** in G1 following DNA damage. In order to investigate a proposed novel role for p53 as a **checkpoint** at mitosis following disruption of the mitotic **spindle**, we have used time-lapse videomicroscopy to show that both p53+/+ and p53-/- murine fibroblasts treated with the **spindle** drug nocodazole undergo transient arrest at mitosis for the same length of time. Thus, p53 does not participate in **checkpoint** function at mitosis. However, p53 does play a critical role in nocodazole-treated cells which have exited mitotic arrest without undergoing cytokinesis and have thereby adapted. We have determined that in nocodazole-treated, adapted cells, p53 is required during a specific time window to prevent cells from reentering the cell cycle and initiating another round of DNA synthesis. Despite having 4N DNA content, adapted cells are similar to G1 cells in that they have upregulated cyclin E expression and hypophosphorylated Rb protein. The mechanism of the p53-dependent arrest in nocodazole-treated adapted cells requires the cyclin-dependent kinase inhibitor p21, as p21-/- fibroblasts fail to arrest in response to nocodazole treatment and become polyploid. Moreover, p21 is required to a similar extent to maintain cell cycle arrest after either nocodazole treatment or irradiation. Thus, the p53-dependent **checkpoint** following **spindle** disruption functionally overlaps with the p53-dependent **checkpoint** following DNA damage.

L9 ANSWER 130 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1998:88356 BIOSIS
DN PREV199800088356
TI Human papillomavirus oncoproteins E6 and E7 independently abrogate the mitotic **spindle checkpoint**.
AU Thomas, Jennifer T.; Laimins, Laimonis A. (1)
CS (1) Dep. Microbiology-Immunol., Northwestern Univ. Med. Sch., 303 E. Chicago Ave., Chicago, IL 60611 USA
SO Journal of Virology, (Feb., 1998) Vol. 72, No. 2, pp. 1131-1137.
ISSN: 0022-538X.
DT Article
LA English
AB The E6 and E7 genes of the high-risk human papillomavirus (HPV) types encode oncoproteins, and both act by interfering with the activity of

cellular **tumor** suppressor proteins. E7 proteins act by associating with members of the retinoblastoma family, while E6 increases the turnover of p53. p53 has been implicated as a regulator of both the G1/S cell cycle **checkpoint** and the mitotic **spindle checkpoint**. When fibroblasts from p53 knockout mice are treated with the **spindle** inhibitor nocodazole, a rereplication of DNA occurs without transit through mitosis. We investigated whether E6 or E7 could induce a similar loss of mitotic **checkpoint** activity in human keratinocytes. Recombinant retroviruses expressing high-risk E6 alone, E7 alone, and E6 in combination with E7 were used to infect normal human foreskin keratinocytes (HFKs). Established cell lines were treated with nocodazole, stained with propidium iodide, and analyzed for DNA content by flow cytometry. Cells infected with high-risk E6 were found to continue to replicate DNA and accumulated an octaploid (8N) population. Surprisingly, expression of E7 alone was also able to bypass this **checkpoint**. Cells expressing E7 alone exhibited increased levels of p53, while those expressing E6 had significantly reduced levels. The p53 present in the E7 cells was active, as increased levels of p21 were observed. This suggested that E7 bypassed the mitotic **checkpoint** by a p53-independent mechanism. The levels of MDM2, a cellular oncoprotein also implicated in control of the mitotic **checkpoint** , were significantly elevated in the E7 cells compared to the normal HFKs. In E6-expressing cells, the levels of MDM2 were undetectable. It is possible that abrogation of Rb function by E7 or increased expression of MDM2 contributes to the loss of mitotic **spindle checkpoint** control in the E7 cells. These findings suggest mechanisms by which both HPV oncoproteins contribute to genomic instability at the mitotic **checkpoint**.

L9 ANSWER 131 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1998:73429 BIOSIS
DN PREV199800073429
TI The human papillomavirus-16 E6 oncoprotein decreases the vigilance of mitotic checkpoints.
AU Thompson, David A.; Belinsky, Glenn; Chang, Ted H.-T.; Jones, D. Leanne; Schlegel, Robert; Munger, Karl (1)
CS (1) Dep. Pathol., Harv. Med. Sch., 200 Longwood Ave., Boston, MA 02115 USA
SO Oncogene, (Dec. 18, 1997) Vol. 15, No. 25, pp. 3025-3035. ISSN: 0950-9232.
DT Article
LA English
AB The E6 and E7 proteins of the high risk human papillomaviruses (HPVs) are consistently expressed in HPV-positive cervical carcinomas. We investigated the ability of HPV-16 E6 and E7 to disrupt mitotic checkpoints in normal diploid human cells. Acute expression of HPV-16 E6, but not HPV-16 E7, decreased the fidelity of multiple checkpoints controlling entry into and exit from mitosis. After irradiation, nearly 50% of cells containing HPV-16 E6 readily entered mitosis as opposed to less than 10% of control cells. Consistent with this, asynchronous populations of cells expressing HPV-16 E6 had increased cdc2-associated histone H1 kinase activity relative to control populations. In addition, HPV-16 E6 increased sensitivity to chemically-induced S-phase premature mitosis and decreased mitotic **spindle** assembly **checkpoint** function relative to control populations. HPV-16 E6 mutants with a reduced ability to target p53 for degradation were unable to abrogate mitotic checkpoints, suggesting a possible mechanism by which HPV-16 E6 disrupts mitotic checkpoints. Expression of a mutant p53 gene yielded an intermediate phenotype relative to HPV-16 E6, generating moderate increases in sensitivity to chemically-induced S-phase PCC and mitotic **spindle** disruption and a heightened propensity to enter mitosis after irradiation.

L9 ANSWER 132 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1997:441508 BIOSIS

DN PREV199799740711
TI Loss of RB and MTS1/CDKN2 (p16) expression in human sarcomas.
AU Cohen, Jill A.; Geradts, Joseph (1)
CS (1) Dep. Pathol. Lab. Med., CB 7525, Univ. North Carolina Sch. Med., Chapel Hill, NC 27599-7525 USA
SO Human Pathology, (1997) Vol. 28, No. 8, pp. 893-898.
ISSN: 0046-8177.
DT Article
LA English
AB The product of the MTS1/CDKN2 gene (p16) and the retinoblastoma protein (pRB) inhibit cell cycle progression at the late G1 **checkpoint**. The absence of functional p16 or pRB has been identified in a variety of human tumors but has not been well studied in mesenchymal neoplasia. Using an immunohistochemical approach, the authors identified abnormal expression of either p16 or RB in 16 and 14 of 59 sarcomas, respectively, for an overall abnormality rate of 51%. Specific rates of abnormality varied by histological subtype, with leiomyosarcomas most commonly affected by loss of either **tumor**-suppressor gene product. There was no significant correlation between p16 or R.B expression and overall grade, mitotic grade, or **tumor** progression for sarcomas. In contrast, no fibromatoses and other **spindle** cell neoplasms of low malignant potential displayed abnormal p16 expression, and only 4 of 23 cases showed loss of pRB expression. These data show that aberrant expression of p16/pRB is one of the most common molecular derangements in sarcomagenesis.

L9 ANSWER 133 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1997:422393 BIOSIS
DN PREV199799721596
TI A novel thyroid hormone analog binds to tubulin and induces apoptosis and mitotic arrest in human **cancer** cells.
AU Chen, Xiaoying; Knapp, A. Merrill; Laderoute, Keith L.
CS Pharmaceutical Discovery Div., SRI International, 333 Ravenswood Ave., Menlo Park, CA 94025 USA
SO FASEB Journal, (1997) Vol. 11, No. 9, pp. A1391.
Meeting Info.: 17th International Congress of Biochemistry and Molecular Biology in conjunction with the Annual Meeting of the American Society for Biochemistry and Molecular Biology San Francisco, California, USA August 24-29, 1997
ISSN: 0892-6638.
DT Conference; Abstract
LA English

L9 ANSWER 134 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1997:295894 BIOSIS
DN PREV199799595097
TI Disregulation of mitotic checkpoints and regulatory proteins following acute expression of SV40 large T antigen in diploid human cells.
AU Chang, Ted Hung-Tse; Ray, F. Andrew; Thompson, D. Alan; Schlegel, Robert (1)
CS (1) Dep. Mol. Cell. Toxicol., Harvard Sch. Public Health, 665 Huntington Ave., Boston, MA 02115 USA
SO Oncogene, (1997) Vol. 14, No. 20, pp. 2383-2393.
ISSN: 0950-9232.
DT Article
LA English
AB SV40 large T antigen (T) inactivates the **tumor** suppressor proteins p53 and pRb, and can induce cells to enter DNA replication at inappropriate times. We show here that T also compromises three cell cycle checkpoints that regulate the entry into and exit from mitosis. Human diploid fibroblasts infected with a retrovirus expressing T displayed an attenuated radiation-induced mitotic delay, were more susceptible to chemical-induced uncoupling of mitosis from the completion of DNA replication, and were more likely to exit mitosis and rereplicate their

DNA when mitotic **spindle** assembly was inhibited. Consistent with altered mitotic **checkpoint** control, cells expressing T displayed elevated protein levels and/or associated activities of the mitotic regulatory proteins cyclin A, cyclin B, Cdc25C and p34-cdc2. These changes in mitotic control were evident within 5-10 population doublings after retroviral infection, indicating a direct effect of T expression. Cells acutely infected with the T-expressing retrovirus suffered numerical and structural chromosome aberrations, including increases in aneuploidy, dicentric chromosomes, chromatid exchanges and chromosome breaks and gaps. These findings indicate that T rapidly disrupts mitotic checkpoints that help maintain genomic stability, and suggest mechanisms by which T induces chromosome aberrations and promotes the immortalization and neoplastic transformation of human cells.

L9 ANSWER 135 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1997:216086 BIOSIS
DN PREV199799522590
TI Caffeine induces S-phase apoptosis in cis-diamminedichloroplatinum-treated cells, whereas cis-diamminedichloroplatinum induces a block in G-2/M.
AU Shinomiya, Nariyoshi (1); Takemura, Toshiya; Iwamoto, Kazutsugu; Rokutanda, Makoto
CS (1) Dep. Biol., Natl. Defense Med. Coll., 3-2 Namiki, Tokorozawa, Saitama 359 Japan
SO Cytometry, (1997) Vol. 27, No. 4, pp. 365-373.
ISSN: 0196-4763.
DT Article
LA English
AB Caffeine overrides checkpoints in the G-2 phase of the cell cycle by inhibiting DNA repair at this phase and increases the cytotoxicity of antitumor drugs, such as cis-diamminedichloroplatinum (CODP). The enhanced cell death induced by caffeine is characterized by apoptosis. In this paper, we demonstrate that this apoptotic event occurs in S phase of the cell cycle, whereas CDDP induces a block in G-2/M. DNA histogram analysis revealed that caffeine reduced G-2 arrest in CDDP-treated EL-4 cells. In a synchronous population, the ratio of cyclin B:p34-cdc2 was upregulated just before the cells went into the apoptotic pathway. A rapid increase in DNA fragmentation was detected at 12-24 h, when marked regression of G-2/M phase was observed. Moreover, the degree of DNA fragmentation in CDDP + caffeine-treated cells was not reduced when the cell cycle was arrested at metaphase by exposure to the **spindle**-inhibitor nocodazole. It is possible that execution of the apoptotic program after treatment with caffeine did not require the EL-4 cells to reenter G-1 phase. The apoptotic cell fraction in the group of CDDP + caffeine was recognized as an S population by bivariate analysis of apoptosis and DNA content. These results suggest that enhancement of the apoptotic activity of CDDP-treated cells by caffeine is not a G-1-phase event but an S-phase-specific event, whereas cells were arrested in G-2/M phase, and that it is regulated by G-2 **checkpoint**-related proteins.

L9 ANSWER 136 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1997:177349 BIOSIS
DN PREV199799469062
TI DNA rereplication in the presence of mitotic **spindle** inhibitors in human and mouse fibroblasts lacking either p53 or pRb function.
AU Di Leonardo, Aldo (1); Khan, Shireen Hussain; Linke, Steven P.; Greco, Valentina; Seidita, Gregorio; Wahl, Geoffrey M.
CS (1) Dep. Cell Dev. Biol. "A. Monroy," Univ. Palermo, viale delle Scienze 90128, Palermo Italy
SO Cancer Research, (1997) Vol. 57, No. 6, pp. 1013-1019.
ISSN: 0008-5472.
DT Article
LA English
AB Cell cycle checkpoints are biochemical signal transduction pathways that prevent downstream events from being initiated until upstream processes

are completed. We analyzed whether the p53 or pRb **tumor** suppressors are involved in a **checkpoint**(s) that prevents DNA rereplication in the presence of drugs that interfere with **spindle** assembly. Normal mouse and human fibroblasts arrested with a 4N DNA content when treated with nocodazole and Colcemid, whereas isogeneic p53-deficient or pRb-deficient derivatives became polyploid. Flow cytometric and cytogenetic analyses demonstrated that the polyploidy resulted from genomewide rereplication without an intervening mitosis. Thus, p53 and pRb help maintain normal cell ploidy by preventing DNA rereplication prior to mitotic division.

L9 ANSWER 137 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1997:168361 BIOSIS
DN PREV199799474964
TI The cell cycle - theory and application to **cancer**.
AU Parwaresch, R. (1); Rudolph, P.
CS (1) Institut fuer Haematopathologie, Zentrum Pathologie und angewandte, Krebsforschung der Universitaet, Niemannsweg 11, D-24105 Kiel Germany
SO Onkologie, (1996) Vol. 19, No. 6, pp. 464-472.
ISSN: 0378-584X.
DT General Review
LA English
SL English; German
AB The division cycle of normal mammalian cells is governed by a highly coordinated network of interacting mechanisms that ensure a correct succession of the biochemical and biophysical events culminating in mitosis. A family of specific protein kinases, the Cdks, constitute the motor element of cell cycle progression. Their function is regulated at several levels: 1. association with a cyclin subunit situates their activity in different phases of the cell cycle; 2. sequential phosphorylation and dephosphorylation on specific amino acid residues is required for their final activation; 3. their activity can be modulated by complexing with members of the cyclin-dependent kinase inhibitor family (CdkIs). The latter function to a large extent as effectors of signals emitted by cell surface receptors or internal sensors of defective biochemical and biophysical states termed checkpoints. While the fate of cells is largely influenced by external factors throughout G1 phase, an intrinsic program becomes responsible for cell cycle progression after the passage of the 'restriction point' at the G1/S boundary. This crucial transition is controlled by a **checkpoint** mechanism in which the concerted action of p53 and the retinoblastoma protein may induce either a cell cycle arrest or apoptosis in response to genomic damage. Several other **checkpoint** functions regulate the entry into mitosis by assessing the completion of DNA replication and correct chromosome attachment to the **spindle** apparatus. Finally, the number of possible cell divisions is predetermined by the number of small oligonucleotide repeats at the utmost chromosome ends, the telomeres. **Checkpoint** mechanisms can be disrupted by viral oncoproteins or gene mutations. Loss of their function is likely to result in genomic destabilization and gene amplification, which again may allow for chromosome aberrations and, as several connections link the genome to the cell cycle machinery, may permit unrestrained cell growth. The majority of the cell cycle-related proteins, however, do not qualify for monitoring the proliferative activity or the **tumor** growth fraction. To date, only three proteins: p345 (Ki-67), p170 (topoisomerase II-alpha), and p100 (S-phase protein) have been identified as selective indicators of cellular proliferation. The first two recognize all cell cycle phases except G0, whereas the latter is specifically expressed in S, G2, and M phase cells. Application of antibodies to these proteins in clinical pathology was found to be highly relevant for the prediction of **tumor** biology and clinical courses.

L9 ANSWER 138 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1997:84226 BIOSIS

DN PREV199799375939
TI Dynamic changes in nuclear architecture during mitosis: On the role of protein phosphorylation in **spindle** assembly and chromosome segregation.
AU Nigg, Erich A. (1); Blangy, Anne; Lane, Heidi A.
CS (1) Dep. Molecular Biol., Sci. II, Univ. Geneva, 30 Quai Ernest-Ansermet, CH-1211 Geneva 4 Switzerland
SO Experimental Cell Research, (1996) Vol. 229, No. 2, pp. 174-180. ISSN: 0014-4827.
DT General Review
LA English
AB During mitosis, the vertebrate cell nucleus undergoes profound changes in architecture. At the onset of mitosis, the nuclear envelope breaks down, the nuclear lamina is depolymerized, and interphase chromatin is condensed to chromosomes. Concomitantly, cytoplasmic microtubules are reorganized into a mitotic **spindle** apparatus, a highly dynamic structure required for the segregation of sister chromatids. Many of the above events are controlled by reversible phosphorylation. Hence, our laboratory is interested in characterizing the kinases involved in promoting progression through mitosis and in identifying their relevant substrates. Prominent among the kinases responsible for regulating entry into mitosis is the Cdc2 kinase, the first member of the cyclin dependent kinase (Cdk) family. Recently, we found that Cdc2 phosphorylates HsEg5, a human kinesin-related motor protein associated with centrosomes and the **spindle** apparatus. Our results indicate that phosphorylation regulates the association of HsEg5 with the mitotic **spindle** and that the function of this plus-end directed motor is essential for centrosome separation and bipolar **spindle** formation. Another kinase implicated in regulating progression through mitosis is Plk1 (polo-like kinase 1), the human homologue of the Drosophila gene product "polo." By antibody microinjection we have found that Plk1 is required for the functional maturation of centrosomes and hence for entry into mitosis. Furthermore, we found that microinjected anti-Plk1 antibodies caused a more severe block to cell cycle progression in diploid fibroblasts than in immortalized **tumor** cells. This observation hints at the existence of a **checkpoint** linking Cdc2 activation to the presence of functional centrosomes.

L9 ANSWER 139 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1997:39883 BIOSIS
DN PREV199799331871
TI Cell cycle checkpoints: Preventing an identity crisis.
AU Elledge, Stephen
CS Dep. Biochemistry, Howard Hughes Med. Inst., Baylor Coll. Med., One Baylor Plaza, Houston, TX 77030 USA
SO Science (Washington D C), (1996) Vol. 274, No. 5293, pp. 1664-1672. ISSN: 0036-8075.
DT Article
LA English
AB Cell cycle checkpoints are regulatory pathways that control the order and timing of cell cycle transitions and ensure that critical events such as DNA replication and chromosome segregation are completed with high fidelity. In addition, checkpoints respond to damage by arresting the cell cycle to provide time for repair and by inducing transcription of genes that facilitate repair. **Checkpoint** loss results in genomic instability and has been implicated in the evolution of normal cells into **cancer** cells. Recent advances have revealed signal transduction pathways that transmit **checkpoint** signals in response to DNA damage, replication blocks, and **spindle** damage.
Checkpoint pathways have components shared among all eukaryotes, underscoring the conservation of cell cycle regulatory machinery.

L9 ANSWER 140 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1996:539985 BIOSIS

DN PREV199699262341
TI Identification of a human mitotic **checkpoint** gene: hsMAD2.
AU Li, Yong; Benezra, Robert (1)
CS (1) Cell Biol. Genet. Program, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021 USA
SO Science (Washington D C), (1996) Vol. 274, No. 5285, pp. 246-248. ISSN: 0036-8075.
DT Article
LA English
AB In Saccharomyces cerevisiae, MAD2 is required for mitotic arrest if the **spindle** assembly is perturbed. The human homolog of MAD2 was isolated and shown to be a necessary component of the mitotic **checkpoint** in HeLa cells by antibody electroporation experiments. Human, or Homo sapiens, MAD2 (hsMAD2) was localized at the kinetochore after chromosome condensation but was no longer observed at the kinetochore in metaphase, suggesting that MAD2 might monitor the completeness of the **spindle**-kinetochore attachment. Finally, T47D, a human breast **tumor** cell line that is sensitive to taxol and nocodazole, had reduced MAD2 expression and failed to arrest in mitosis after nocodazole treatment. Thus, defects in the mitotic **checkpoint** may contribute to the sensitivity of certain tumors to mitotic **spindle** inhibitors.

L9 ANSWER 141 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1996:464767 BIOSIS
DN PREV199699187123
TI Induction of apoptosis by tamoxifen-activation of a p53-estrogen receptor fusion protein expressed in E1A and T24 H-ras transformed p53-/-mouse embryo fibroblasts.
AU Vater, Carol A. (1); Bartle, Laura M.; Dionne, Cheryl A.; Littlewood, Trevor D.; Goldmacher, Victor S.
CS (1) Apoptosis Technol., Inc., 148 Sidney St., Cambridge, MA 02139-4239 USA
SO Oncogene, (1996) Vol. 13, No. 4, pp. 739-748. ISSN: 0950-9232.
DT Article
LA English
AB A fusion gene consisting of wild-type p53 linked to a modified ligand binding domain of the murine estrogen receptor has been constructed and should be a useful toot for studying controlled activation of wild-type p53 function in a variety of experimental cell systems. The protein product of this gene, p53ER, is expressed in cells constitutively but is not functional unless associated with tamoxifen or 4-hydroxytamoxifen. p53ER was introduced into p53-deficient mouse embryo fibroblasts (MEFs)) expressing the E1A and T24 H-ras oncogenes. Activation of p53 in these transformed cells by the addition of tamoxifen or 4-hydroxytamoxifen resulted in apoptosis. In addition to engaging the apoptotic machinery, the tamoxifen-activated fusion protein exhibited other functions characteristic of wild-type p53, such as induction of WAF1 and MDM2 gene expression and activation of the p53-dependent **spindle** **checkpoint** in cells treated with nocodazote. Activation of p53ER expressed in p53-positive MEFs coexpressing E1A and ras had, at most, only a small cytotoxic effect. When three cell lines of transformed p53+/+ fibroblasts not expressing p53ER were tested for sensitivity to the DNA-damaging drug doxorubicin, the p53+/+ clones displayed either comparable sensitivity, or at most an increase in drug sensitivity of less than fourfold, as compared to several p53-/- cell lines. Our data show that restoration of wild-type p53 activity is sufficient to trigger apoptosis in p53-/- MEFs transformed with E1A and T24 H-ras and suggest that rare propagable clones of p53-normal MEFs expressing the E1A and T24 H-ras oncogenes have suffered compensatory alterations that compromise the ability to undergo p53-dependent apoptosis.

L9 ANSWER 142 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1996:434597 BIOSIS

DN PREV199699148203
TI Activation of the Budding yeast **spindle** assembly **checkpoint** without mitotic **spindle** disruption.
AU Hardwick, Kevin G.; Weiss, Eric; Luca, Francis C.; Winey, Mark; Murray, Andrew W. (1)
CS (1) Dep. Physiol., Univ. California, San Francisco, CA 94143-0444 USA
SO Science (Washington D C), (1996) Vol. 273, No. 5277, pp. 953-956. ISSN: 0036-8075.
DT Article
LA English
AB The **spindle** assembly **checkpoint** keeps cells with defective spindles from initiating chromosome segregation. The protein kinase Mps1 phosphorylates the yeast protein Mad1p when this **checkpoint** is activated, and the overexpression of Mps1p induces modification of Mad1p and arrests wild-type yeast cells in mitosis with morphologically normal spindles. **Spindle** assembly **checkpoint** mutants overexpressing Mps1p pass through mitosis without delay and can produce viable progeny, which demonstrates that the arrest of wild-type cells results from inappropriate activation of the **checkpoint** in cells whose **spindle** is fully functional. Ectopic activation of cell-cycle checkpoints might be used to exploit the differences in **checkpoint** status between normal and **tumor** cells and thus improve the selectivity of chemotherapy.

L9 ANSWER 143 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1995:455994 BIOSIS
DN PREV199598470294
TI Mice Lacking p21-CIP1/WAF1 Undergo Normal Development, but Are Defective in G1 **Checkpoint** Control.
AU Deng, Chuxia (1); Zhang, Pumin; Harper, J. Wade; Elledge, Stephen J.; Leder, Philip
CS (1) Lab. Biochem. Metabolism, Natl. Inst. Diabetes, Digestive Kidney Dis., Natl. Inst. Health, Bethesda, MD 20892 USA
SO Cell, (1995) Vol. 82, No. 4, pp. 675-684. ISSN: 0092-8674.
DT Article
LA English
AB p21-CIP1/WAF1 is a CDK inhibitor regulated by the **tumor** suppressor p53 and is hypothesized to mediate G1 arrest. p53 has been suggested to derive anti-oncogenic properties from this relationship. To test these notions, we created mice lacking p21-CIP1/WAF1. They develop normally and (unlike p53-/- mice) have not developed spontaneous malignancies during 7 months of observation. Nonetheless, p21-/- embryonic fibroblasts are significantly deficient In their ability to arrest in G1 in response to DNA damage and nucleotide pool perturbation. p21-/- cells also exhibit a significant growth alteration in vitro, achieving a saturation density as high as that observed in p53-/- cells. In contrast, other aspects of p53 function, such as thymocytic apoptosis and the mitotic **spindle checkpoint**, appear normal. These results establish the role of p21-CIP1/WAF1 in the G1 **checkpoint** , but suggest that the antiapoptotic and the anti-oncogenic effects of p53 are more complex.

L9 ANSWER 144 OF 144 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1995:168380 BIOSIS
DN PREV199598182680
TI A p53-Dependent Mouse **Spindle Checkpoint**.
AU Cross, Shawn M.; Sanchez, Carissa A.; Morgan, Catherine A.; Schimke, Melana K.; Ramel, Stig; Idzerda, Rejean L.; Raskind, Wendy H.; Reid, Brian J. (1)
CS (1) Dep. Med., Univ. Washington, Seattle, WA 98195 USA
SO Science (Washington D C), (1995) Vol. 267, No. 5202, pp. 1353-1356. ISSN: 0036-8075.
DT Article

LA English
AB Cell cycle checkpoints enhance genetic fidelity by causing arrest at specific stages of the cell cycle when previous events have not been completed. The **tumor** suppressor p53 has been implicated in a G-1 **checkpoint**. To investigate whether p53 also participates in a mitotic **checkpoint**, cultured fibroblasts from p53-deficient mouse embryos were exposed to **spindle** inhibitors. The fibroblasts underwent multiple rounds of DNA synthesis without completing chromosome segregation, thus forming tetraploid and octaploid cells. Deficiency of p53 was also associated with the development of tetraploidy in vivo. These results suggest that murine p53 is a component of a **spindle checkpoint** that ensures the maintenance of diploidy.

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FILE 'BIOSIS' ENTERED AT 15:47:52 ON 25 JUL 2003

L1	1399	S	MAD
L2	167	S	CDC20
L3	4	S	L1 AND L2
L4	0	S	MITOSIS 3A ARREST 3A DEFICIENT
L5	0	S	MITOSIS ARREST DIFICIENT
L6	0	S	MITOSIS ARREST DEFICIENT
L7	631	S	SPINDLE AND CHECKPOINT
L8	890800	S	CANCER OR TUMOUR OR TUMOR
L9	144	S	L7 AND L8

=>